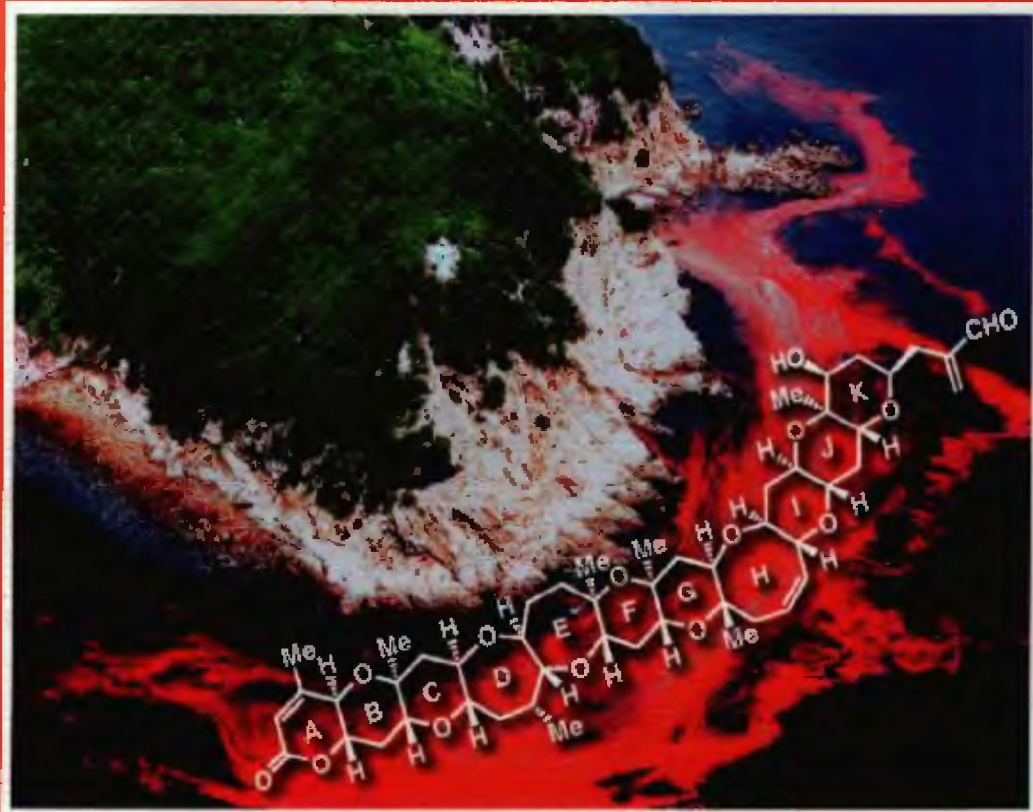
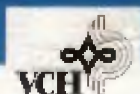


K. C. NICOLAOU, E. J. SORENSEN

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K. C. Nicolaou and
E. J. Sorensen

Targets, Strategies, Methods

With a Foreword by
E. J. Corey



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K. C. Nicolaou, Ph. D.
Erik J. Sorensen, Ph. D.

Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, CA 92037
USA

and Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093
USA

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Back cover: Structure of vitamin B₁₂.

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Foreword

If a definitive history of twentieth century science is ever written, one of the highlights may well be a chapter on the chemical synthesis of complex molecules, especially the total synthesis of naturally occurring substances. I state this, while trying to be as objective as possible, because it is not easy to find an area of scientific work that encompasses so many interesting elements. I shall name just a few: great complexity and variety; challenge verging on impossibility; demand for both mental and manipulative rigor, and for dedication, persistence, and hard work; never-ending frontiers for discovery and never-ending advances in sophistication; unlimited opportunities for intellectual excitement and satisfaction; strong coupling not only with all areas of chemistry, but also with biology and medicine; relevance, at a very fundamental level to human well-being, health, and education.

As I read a prepublication draft of "*Classics in Total Synthesis*", all of these general characteristics of synthetic research assumed a reality and sharpness that I had not expected, partly because I was already familiar with each of the thirty-seven classics in this collection. It was a sheer delight to revisit each of these triumphs guided by the wise insights and analyses found throughout this book. There is a nice balance between the underlying historical material and the design and execution aspects of each synthesis. In addition, the broad perspectives on synthesis, supplemented in each section by detailed explanations of the key features of each synthesis, lead to a presentation that is both clear and stimulating. The pedagogy is effective.

As mentioned by the authors in their preface, the achievements in total synthesis have been so numerous and so important that it is clearly impossible to include them all in a single volume. My hope is that "*Classics in Total Synthesis*" will be successful and that it will be followed by a continuing series. Such a collection will add to our reading pleasure and further encourage and inspire new generations of chemists to dare the impossible (or even the unfashionable). There is much still to be learned and to be discovered. Humanity will be enriched beyond measure if the twenty-first century is a period of continued vigorous development of synthetic chemistry.

I would like to congratulate Professor Nicolaou and Dr. Sorensen on this fine addition to the literature of synthetic chemistry and to wish them well in their further work as scientists and as authors. May the journey in total synthesis follow the Ithaca model (page 16).

E. J. Corey
Harvard University
30 October 1995

Abbreviations

Ac	acetyl	GC	gas chromatography
acac	acetylacetonyl	HETE	hydroxyeicosatetraenoic
AD	asymmetric dihydroxylation	hfc	3-(heptafluoropropyl)hydroxymethylene-d-camphorato
AIBN	2,2'-azobisisobutyronitrile	HMPA	hexamethylphosphoramide
BBEDA	<i>N,N'</i> -bis(benzylidene)ethylenediamine	HMG	hydroxymethylglutaryl
9-BBN	9-borabicyclo[3.3.1]nonane	HPLC	high-pressure liquid chromatography
BINAL-H	2,2'-dihydroxy-1,1'-binaphthylaluminum hydride	HWE	Horner-Wadsworth-Emmons
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	Im (imid.)	imidazole
Bn	benzyl	IND	indoline
BOC (<i>t</i> -BOC)	<i>tert</i> -butoxycarbonyl	Ipc	isopinocampheyl
BOM	benzyloxymethyl	KHMDS	potassium bis(trimethylsilyl)amide
BTMSA	bis(trimethylsilyl)acetylene	LDA	lithium diisopropylamide
Bz	benzoyl	LHMDS	lithium bis(trimethylsilyl)amide
18-C-6	18-crown-6	<i>m</i> CPBA	3-chloroperoxybenzoic acid
Cbz	benzyloxycarbonyl	MEM	2-methoxyethoxymethyl
CHD	coronary heart disease	MOM	methoxymethyl
CoA	coenzyme A	Ms	methanesulfonyl
COD	1,5-cyclooctadiene	NaHMDS	sodium bis(trimethylsilyl)amide
Cp	cyclopentadienyl	NB	2-nitrobenzyl
CSA	10-camphorsulfonic acid	<i>p</i> NB	4-nitrobenzyl
Cy (Cy-Hex)	cyclohexyl	NBS	<i>N</i> -bromosuccinimide
DAIB	3- <i>exo</i> -(dimethylamino)isoborneol	NCS	<i>N</i> -chlorosuccinimide
DAST	diethylaminosulfur trifluoride	NIS	<i>N</i> -iodosuccinimide
dba	<i>trans,trans</i> -dibenzylideneacetone	NMM	4-methylmorpholine
DBN	1,5-diazabicyclo[4.3.0]non-5-ene	NMO	4-methylmorpholine <i>N</i> -oxide
DBS	5-dibenzosuberyl	NMP	1-methyl-2-pyrrolidinone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	NMR	nuclear magnetic resonance
DCBI	<i>N,N'</i> -dicyclohexyl- <i>O</i> -benzylisourea	Nu	nucleophile
DCC	1,3-dicyclohexylcarbodiimide	PCC	pyridinium chlorochromate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	PDC	pyridinium dichromate
<i>de</i>	diastereomeric excess	PG	prostaglandin
DEAD	diethyl azodicarboxylate	Ph	phenyl
DEIPS	diethylisopropylsilyl	PHAL	phthalazine
DET	diethyl tartrate	Phth	phthalimido
DHP	3,4-dihydro-2 <i>H</i> -pyran	Piv	pivaloyl
DHQ	dihydroquinine	PMB	4-methoxybenzyl
DHQD	dihydroquinidine	PNNP	<i>N,N'</i> -bis(1-phenylethyl)- <i>N,N'</i> -bis-(diphenylphosphino)ethylenediamine
DIAD	diisopropyl azodicarboxylate	PPTS	pyridinium 4-toluenesulfonate
Dibal-H	diisobutylaluminum hydride	psi	pounds per square inch
DIOP	2,3- <i>O</i> -isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane	pyr. (pyr, py)	pyridine
DiPAMP	1,2-bis(<i>o</i> -anisylphenylphosphino)ethane	PYR	diphenylpyrimidine
DIPT	diisopropyl tartrate	Ra-Ni	Raney nickel
DMA	<i>N,N</i> -dimethylacetamide	Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
4-DMAP	4-dimethylaminopyridine	SAE	Sharpless Asymmetric Epoxidation
(DMAP)		SEM	2-(trimethylsilyl)ethoxymethyl
DME	ethylene glycol dimethyl ether	Sia	siamyl
DMF	<i>N,N</i> -dimethylformamide	TBAF	tetra- <i>n</i> -butylammonium fluoride
DMS	dimethyl sulfide	TBAI	tetra- <i>n</i> -butylammonium iodide
DMSO	dimethyl sulfoxide	TBS	<i>tert</i> -butyldimethylsilyl
DNA	deoxyribonucleic acid	TEOC	2-(trimethylsilyl)ethoxycarbonyl
L-DOPA	3-(3,4-dihydroxyphenyl)-L-alanine	TES	triethylsilyl
DPC	dipyridine chromium(vi) oxide	Tf	trifluoromethanesulfonyl
DTBMS	di(<i>tert</i> -butyl)methylsilyl	TFA	trifluoroacetic acid
EDC (EDCI)	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride	TFAA	trifluoroacetic anhydride
<i>e</i>	electron	THF	tetrahydrofuran
<i>ee</i>	enantiomeric excess	THP	tetrahydropyran
EE	1-ethoxyethyl	TIPS	triisopropylsilyl
Et-DuPHOS	1,2-bis(2',5'-diethylphospholano)ethane	TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
Fmoc	9-fluorenylmethoxycarbonyl	TMS	trimethylsilyl
FPP	farnesyl pyrophosphate	TPAP	tetra- <i>n</i> -propylammonium perruthenate
		TPS	<i>tert</i> -butyldiphenylsilyl
		trityl	triphenylmethyl
		Ts	4-toluenesulfonyl

Preface

This book is intended to be an historical record of some of the greatest total syntheses of all time. We also hope that it will serve as a teaching and learning tool for teachers, students, and practitioners of organic synthesis. In Chapter 1, the reader will find a discussion on the philosophy, purpose, and use of total synthesis. In each of the remaining 36 chapters, we describe the total synthesis of a natural product. Through the examples chosen, an effort was made to trace the evolution of the science of total synthesis to its present state and to demonstrate the utility of important chemical reactions in the construction of target organic molecules. Despite the diversity of structures, each total synthesis is presented in a unifying pedagogical format, which hopefully distinguishes this book from any other.

In the *Introduction* section of each chapter, the background and biological action of the target molecule is discussed, and the important synthetic reactions involved in the synthesis are presented. Following the introduction is the *Retrosynthetic Analysis and Strategy* section, in which the target molecule is analyzed retrosynthetically to show and explain the evolution of the synthetic strategy. In the *Total Synthesis* section, the execution of the synthesis is discussed, with special emphasis placed on tactics, efficiency, selectivity, stereochemistry, and synthetic maneuvering. The *Conclusion* section summarizes in a concise manner the main findings and impact of the total synthesis.

Throughout each chapter, clear structures, schemes, and figures accompany the text. Mechanism, reactivity, selectivity, and stereochemistry are especially addressed. Special emphasis is also placed on introducing both the logic of total synthesis and the rationale for the invention and use of important synthetic methods. In particular, we amplify the most important developments in asymmetric synthesis, catalysis, cyclization reactions, and organometallic chemistry.

This volume is based partly on the lecture notes of K. C. N. that were used for teaching courses at the University of Pennsylvania, the University of California, San Diego, and The Scripps Research Institute. We apologize sincerely to those whose brilliant works have been left out owing to the inevitable closing of the curtain and hope that in the event of a second volume we can rectify these omissions. We also apologize in advance for the inevitable errors that a volume of this size may contain, and welcome constructive comments from our readers in order to correct such errors in future editions.

It is our hope that this book will find its way into the hands of every student of organic synthesis and that it will serve both to edu-

cate and inspire. If we can excite and stimulate a new generation of chemists in the direction of organic synthesis, then we will be satisfied that a major part of our goal has been reached.

We wish to thank Janise L. Petrey for her tenacity, skill, and patience in processing the many and fragmentary versions of this book. We would also like to thank Alan Nadin for his thoughtful comments and useful suggestions on various aspects of the manuscript. We are grateful to Chris F. Claiborne, Otto Gräther, R. Kip Guy, John I. Trujillo, and Eddy W. Yue for their assistance and for checking the references. We thank Professors Charlie L. Perrin, Jay S. Siegel, and Emmanuel A. Theodorakis for useful discussions and suggestions, and Vicky Nielsen for her managerial skills in keeping us all together. We owe our many thanks to Georgette, Colette, Alex, Chris, and P.J. Nicolaou and Karla Sorensen for their support and patience during this odyssey, and we offer our apologies for not being there when we should have been ...

Our sincere appreciation goes to all the members of the K.C.N. group whose dedication, brilliance, and diverse ethnic background have made this group's contributions both possible and enjoyable.

Finally, we would like to dedicate this book to Professor E.J. Corey, whose teachings and research have helped shape the science of organic synthesis and the art of total synthesis as we know it today.

La Jolla
October 1995

K.C. Nicolaou
E.J. Sorensen

About the Authors



K. C. Nicolaou was born in 1946 in Cyprus. He studied chemistry at the University of London (B. Sc., 1969; Ph.D., 1972), Columbia University (postdoctoral research) and Harvard University (postdoctoral research). Between 1976 and 1989 he was a faculty member at the University of Pennsylvania. He currently holds joint appointments at The Scripps Research Institute, where he is the Darlene Shiley Professor of Chemistry and Chairman of the Department of Chemistry, and at the University of California, San Diego, where he is Professor of Chemistry. His research interests span the areas of synthetic organic chemistry, bioorganic chemistry, molecular design, and the chemistry and biology of natural products.

Erik J. Sorensen was born in 1966 in Oneida, New York. He graduated from Syracuse University with a B.A. in chemistry. He received his Ph.D. degree in chemistry from the University of California, San Diego in 1995 working under the guidance of Professor K.C. Nicolaou. His research interests are in the areas of total synthesis and reaction engineering.



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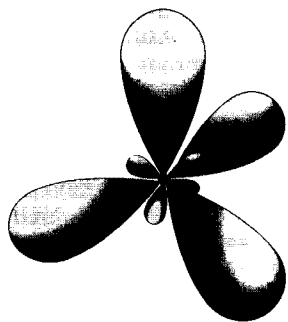
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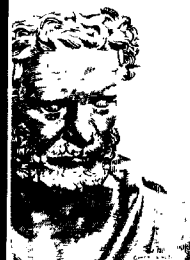


Introduction: Constructing the Molecules of Nature

The world is made of two parts, the full (pleres, stereon) and the empty, the vacuum (cenon, manon). The fullness is divided into small particles called atoms (atomon, that cannot be cut, indivisible). The atoms are infinite in number, eternal, absolutely simple; they are all alike in quality but differ in shape, order, and position. Every substance, every single object, is made up of those atoms, the possible combinations of which are infinite in an infinity of ways. The objects exist as long as the atoms constituting them remain together; they cease to exist when their atoms move away from one another. The endless changes of reality are due to the continual aggregation and disaggregation of atoms.

Democritus, fifth century B.C.¹

ΔΗ
ΜΟ
ΚΡΙ
ΤΟΣ



Democritus

With remarkable accuracy, Democritus in the fifth century B.C. set the stage for modern chemistry. His atomic theory of matter, which he formulated without experimental verification, still stands, more or less intact, and encapsulates the profound truth that nature's stunning wealth boils down to atoms and molecules. As science uncovers the mysteries of the world around us, we stand ever more in awe of nature's ingenious molecular designs and biological systems: nucleic acids, saccharides, proteins, and secondary metabolites are four classes of wondrous molecules that nature synthesizes with remarkable ease, and uses with admirable precision in the assembly and function of living systems.

The chemical synthesis of nature's molecules without the aid of enzymes often presents formidable challenges to human ingenuity and skill. While chemical processes for the synthesis of oligonucleotides and peptides are now well developed and quite routine, nature's secondary metabolites, commonly known as natural products, are not always easy to construct in the laboratory. Their structures exist in an almost infinite range of complexity and stability and, therefore, often present distinct synthetic problems which require unique strategies and tactics for their solution. It is this almost unlimited variation in structure and the constant discovery of new molecular constructs that keeps the field of natural products synthesis so attractive and vibrant. The dazzling biological properties exhibited by many natural products and the attendant opportunities these molecules offer for probing biological questions also serve as major attractions in this field of investigation. The constructing of nature's molecules in the laboratory from atoms and/or simple molecules, a process often known as *total synthesis*, is one of the most demanding human practices. For this reason, training in this field is considered highly valuable, attractive, and rewarding, particularly to those who enjoy challenge and those who wish to acquire the awesome power of creating new chemical entities. In order to put total synthesis into proper perspective, a brief overview of synthetic chemistry would be instructive.

1.1 *Synthetic Chemistry and Total Synthesis*

Synthetic chemistry (from the Greek word *synthesis* = the process of putting together) is the science of constructing molecules from atoms and/or (usually) simpler molecules. The discipline may be subdivided, according to the molecules involved, into *synthetic organic chemistry* and *synthetic inorganic chemistry*. The term *organic synthesis* is often used – maybe incorrectly in strict terms despite common usage and history² – to mean the same as *synthetic organic chemistry*. Even the phrase *chemical synthesis* is sometimes used to designate the science of synthetic chemistry, although strictly speaking chemical synthesis is the *process* by which a particular molecule is synthesized in the laboratory.

Total synthesis is the chemical synthesis of a molecule, usually a natural product, from relatively simple starting materials and is to be distinguished from *partial synthesis* or *semisynthesis* which designates the synthesis of a given molecule from an advanced precursor related to it, which may or may not be a natural product itself. Again, the term *total synthesis* has evolved to commonly also mean the science of constructing molecules from simple fragments. For the purposes of this book we will use the broader meanings of these terms.

1.2 The Scope of Organic Synthesis

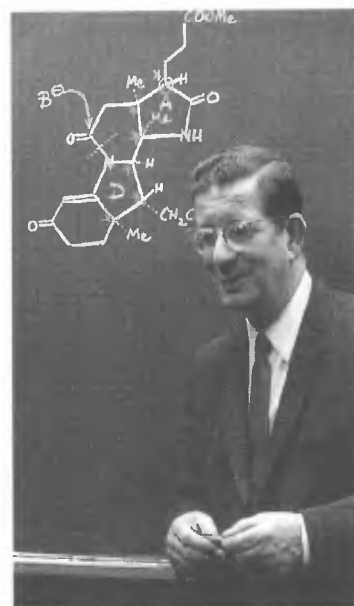
"There is excitement, adventure, and challenge, and there can be great art in organic synthesis." R. B. Woodward³

"The organic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine, and even to create. These added elements provide the touch of artistry which can be included in a cataloging of the basic principles of synthesis but they are very real and extremely important." E. J. Corey⁴

With these words, Woodward and Corey, arguably the two undisputed masters of the art and science of organic synthesis, describe the heart and soul of the subject. The practice and advancement of the field of organic synthesis requires and cultivates some of the most sophisticated virtues and talents of human nature: knowledge, creativity, geometric and artistic perception, stamina, and courage. The centrality of the field of organic synthesis to chemistry in particular, and to the other sciences in general, lies not only in its capacity to deliver substances for further studies and usage, but more significantly in its capacity to create new entities that have not been seen before. The beneficial impact of this field on the health and welfare of society is beyond question, particularly when we make the connection between science and civil progress, as we know it, *via* technology. Several of the millions of organic compounds made over the last century and a half through chemical synthesis are directly linked to important applications in everyday life: pharmaceuticals that can cure or prevent diseases, antifertility agents for population control, insecticides, pesticides, plant and animal hormones to increase food production and nutritional quality, polymers, fabrics, dyes, cosmetics, detergents, photographic and electronic items, and other high-technology materials used in automobile, aircraft, and computer industries, are but some examples of such marvelous inventions.

The impact of this science on biology and medicine in particular merits special mention and is becoming more evident as we approach the next century and as the power of organic synthesis increases with new advances in the field.

The ultimate goal of organic synthesis is to assemble a given organic compound (*target molecule*, usually a combination of atoms from the following group of elements: C, H, O, N, S, P, halogens, and B) from readily available starting materials and reagents in the most efficient way. This process usually begins with the design of a synthetic plan (*strategy, vide infra*) which calls upon various synthetic reactions to address individual synthetic objectives in a certain sequence. If a transformation or a strategic maneuver required by the synthetic plan has not been demonstrated before, the plan must rely on the development of a suitable syn-



R. B. Woodward



E. J. Corey

thetic method or *tactic* to solve the particular problem at hand. Thus, the science of organic synthesis is constantly enriched by new inventions and discoveries pursued deliberately for their own sake or as subgoals within a program directed towards the synthesis of a target molecule.

Despite great strides, organic synthesis should still be viewed as a youthful science. It is also a powerful tool for several other disciplines, including biology, physics, materials science, and medicine. As a field, organic synthesis can be divided into two major areas with further subdivisions as illustrated in Figure 1. The invention, discovery, and development of new synthetic reactions, reagents, and catalysts are grouped under the area of *synthetic methodology*, or *methods-oriented synthesis*, whereas the synthetic pursuit of a defined molecule, natural or designed, is classified under *target-oriented synthesis* (total synthesis is included in this category).

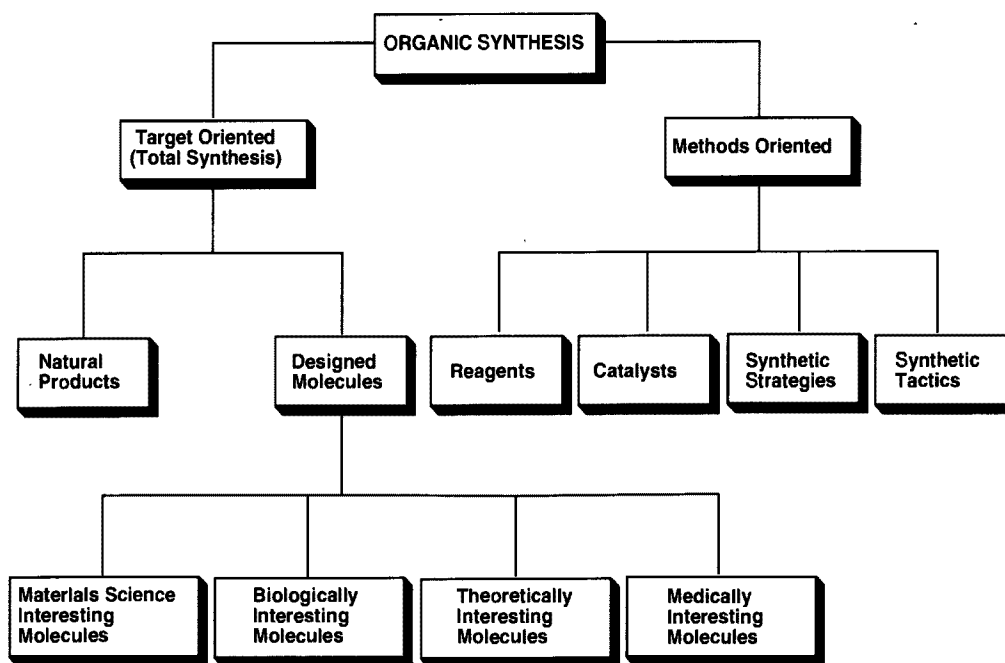


Figure 1. Organic synthesis in perspective.

1.3 A Brief History of Organic Synthesis

Organic synthesis has a long history that can be traced back to ancient times, although at first it was not recognized as such, because it was practiced randomly and strictly heuristically. As a science, organic synthesis is relatively young, its beginning being marked by the rational synthesis of urea [$\text{CO}(\text{NH}_2)_2$] by Wöhler in 1828⁵ (see Figure 2). This synthesis was followed by other milestones such as the synthesis of acetic acid⁶ (Kolbe, 1845), glucose⁷ (Fischer, 1890), α -terpineol⁸ (Perkin, 1904), camphor⁹ (Komppa, 1903; Perkin, 1904), tropinone¹⁰ (Robinson, 1917), haemin¹¹ (Fischer, 1929), equilenin¹² (Bachmann, 1939), pyridoxine hydrochloride¹³ (Folkers, 1939), and quinine¹⁴ (Woodward and Doering, 1944).

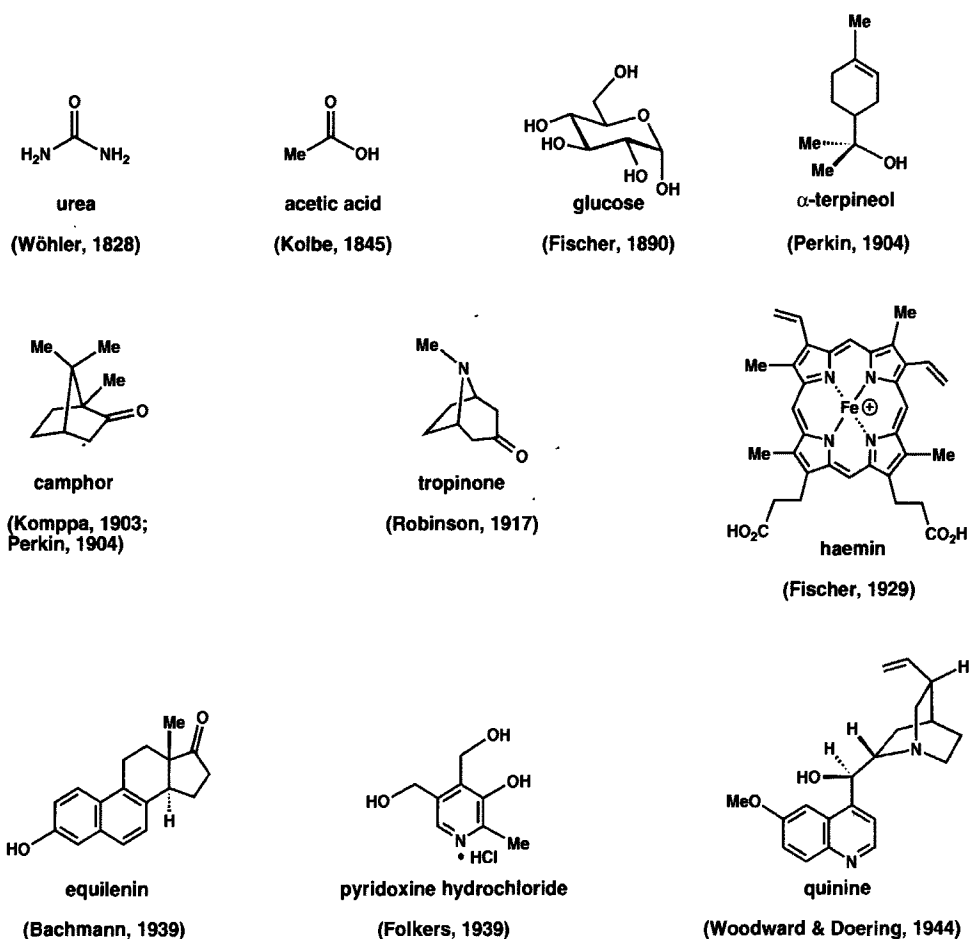


Figure 2. Selected landmark total syntheses of natural products from 1828 to 1944.

Table 1. Nobel Prize winners in organic synthesis and related fields.¹⁵

Year	Nobel Laureate(s)	Work
1902	Emil Fischer	sugars and purine syntheses
1905	Adolf von Baeyer	advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds
1910	Otto Wallach	pioneering work in the field of alicyclic compounds
1912	Victor Grignard and Paul Sabatier	(V. G.) discovery of the Grignard reagent, (P. S.) hydrogenating organic compounds in the presence of finely disintegrated metals
1928	Adolf Windaus	research into the constitution of the sterols and the connection with the vitamins
1930	Hans Fischer	research into the constitution of haemin and chlorophyll and especially for his synthesis of haemin
1937	Walter Haworth and Paul Karrer	(W. H.) investigations on carbohydrates, vitamin C and (P. K.) investigation of carotenoids, flavins, and vitamins A and B ₂
1939	Leopold Ruzicka	work on polymethylenes and higher terpenes
1947	Robert Robinson	investigations on plant products of biological importance, especially the alkaloids
1950	Otto Diels and Kurt Alder	discovery and development of the diene synthesis
1955	Vincent du Vigneaud	work on biochemically important sulfur compounds, especially for the first synthesis of a polypeptide hormone
1963	Karl Ziegler and Giulio Natta	discoveries in the field of the chemistry and technology of high polymers
1965	Robert Burns Woodward	achievements in the art of organic synthesis
1968	H. Gobind Khorana (medicine)	interpretations of the genetic code and its function in protein synthesis
1969	Derek H.R. Barton and Odd Hassel	development of the concept of conformation and its application in chemistry
1975	Vladimir Prelog and John W. Cornforth	(V. P.) stereochemistry of organic molecules and reactions, (J. C.) stereochemistry of enzyme-catalyzed reactions
1979	Herbert C. Brown and Georg Wittig	development of boron (H. C. B.) and phosphorus (G. W.) compounds into important reagents in organic synthesis
1981	Roald Hoffmann and Kenichi Fukui	development of theories concerning the course of chemical reactions
1984	R. Bruce Merrifield	development of methodology for chemical synthesis on a solid matrix
1987	Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen	development and use of molecules with structure-specific interactions of high selectivity
1990	Elias J. Corey	development of the theory and methodology of organic synthesis
1994	George A. Olah	contributions to carbocation chemistry

It was, however, after World War II that organic synthesis and the total synthesis of natural products, in particular, flourished, and many impressive achievements were recorded in rapid succession. With the arrival of R.B. Woodward and his foresight, complex structures fell one after another, total synthesis progressed enormously, and the discipline enjoyed unparalleled respect among the sciences. The theme was taken to even higher levels of sophistication and power by the Corey school. This was achieved by the introduction, on a systematic footing, of the concepts of *retrosynthetic analysis* (*vide infra*) and the emphasis on new synthetic technology as part of the synthetic program.

The importance of organic synthesis to chemistry and its peripheral sciences is clearly evidenced by the frequency with which Nobel Prizes have been awarded to practitioners of this and related fields (Table 1).¹⁵

The drive towards higher levels of achievement in organic synthesis, both in terms of methodology and in terms of complexity of targets, remains unabated. The science is driven by the continuous discovery of novel and complex structures from nature that fascinate and challenge synthetic organic chemists, and by the need to improve our ability to synthesize organic molecules in more efficient and economical ways. Given the almost infinite molecular structures that chemists are likely to discover or imagine and the ever-increasing need for new chemical entities, these driving forces are likely to persist for some time to come. Refinements in analytical, chromatographic, and spectroscopic techniques also contribute to and facilitate the advancement of the science of organic synthesis. Several texts, serial publications, treatises, and journals are dedicated to extensively monitoring the field and no doubt will continue to do so.

1.4 The Practice of Total Synthesis

With its share of glorious moments, setbacks, and frustrations, total synthesis can be compared to the game of chess. The object of this game is to capture the opponent's king by a series of allowed moves played out in such a combination and order as to outmaneuver the opponent. Similarly, in total synthesis the object is to reach the target molecule by a series of reactions (allowed by nature) which have to be carried out in the right sequence to outmaneuver natural barriers. Studying and applying the moves (reactions) to capture the king (make the molecule) then becomes the object of total synthesis.

The practice and elegance of total synthesis involves and depends on the following stages:

1. Selection of the target molecule: natural product, designed molecule
2. Design of the synthetic strategy: retrosynthetic analysis
3. Selection of the reagents and conditions: tactics
4. Experimental execution of the synthesis: dexterity, stamina

Depending on the degree of difficulty encountered in the execution of the synthesis, there is often considerable interplay and readjustment of strategy and tactics before eventual success can be achieved. Thus, one should really add the often inevitable fifth stage – redesign of strategy and tactics – to the above four phases of total synthesis. The elegance and aesthetic appeal of the resulting total synthesis heavily depends on these five stages.

1.5 Target Molecules

"There is no denying (nor should there be any need to deny!) that the sheer sense of challenge posed by a complex molecular target serves to stimulate the creative impulses of the synthetic chemist."

S. J. Danishefsky¹⁶



S. J. Danishefsky

Unless the target molecule is predefined, the selection of such a compound is not a trivial matter, for the selected molecule will determine and direct the path of discovery of new synthetic strategies and methods and new chemical entities. In other words, the target molecule defines to a large extent the research program that lies ahead and the opportunities to be encountered and exploited. Depending on the setting and specific goals of the synthetic chemist, different criteria are used for selecting target molecules. Thus, in academically oriented laboratories where the quest for basic science, competitiveness in the pursuit of excellence, and peer recognition are of primary concern, the target molecules are often selected for their potential to offer opportunities for the development of new synthetic technologies and strategies, to explore and probe biological questions, and to deliver interesting and impressive substances. In industrial laboratories, on the other hand, where emphasis is on commercial exploitation, the target molecules are selected for their potential to lead to practical and profitable applications. Synthetic targets are usually either natural products or designed molecules.

1.6 Natural Products as Synthetic Targets

"The synthesis of substances occurring in Nature, perhaps in greater measure than activities in any other area of organic chemistry, provides a measure of the condition and power of the science."

R. B. Woodward¹⁷

"Nature continues to be exceedingly generous to the synthetic chemist in providing ample opportunity for discovery and creative endeavor of highest magnitude and in surrounding him with an incredible variety of fascinating and complicated structures."

E. J. Corey¹⁸

"Natural product synthesis poses the challenge to consider and develop new pathways of structural transformation. Natural products as targets for synthetic research possess a special fertility in this regard, because the structural channels of biosynthesis are not necessarily the conduits of organic synthesis."

A. Eschenmoser¹⁹



A. Eschenmoser

Ever since synthetic organic chemists realized their ability to assemble molecules from the elements and other simple starting materials, natural products served to fascinate and challenge them. In the classical era, the purpose of a total synthesis was to confirm the molecular structure of a natural product, but as powerful analytical techniques emerged, especially X-ray crystallography and NMR spectroscopy, this is now rarely necessary. In the meantime, however, other reasons for total synthesis have evolved. Amongst the most important are: (a) the challenge, which is often irresistible to those who appreciate and practice the art of synthesizing a naturally occurring substance of novel architecture; (b) the opportunity to discover and develop new synthetic chemistry that will solve, not only the problem under consideration, but also problems of broader interest; (c) the ability to make contributions in biology by providing not only the natural substance when supply is an issue, but also by making available designed molecules that may mimic or inhibit the action of the natural product; (d) the need to develop a process for the large-scale production of the natural product when utility and natural abundance dictate it; and (e) the sheer excitement of the endeavor!

There is wisdom and truth in the statement that natural products, and not designed molecules, provide the ultimate challenges to synthetic chemists. The designer can always adjust his designed targets to fit existing synthetic methods, whereas nature has no mercy on the synthetic chemist. If, for example, a methyl group is present in a molecule in a certain configuration, that group has to be installed in its proper place! Often a seemingly trivial structural feature forces the practitioner to imagine and create new science, for there are no compromises in the science of total synthesis.



D. H. R. Barton



K. B. Sharpless



B. M. Trost

Since the syntheses of urea and acetic acid in 1828 and 1845, respectively, synthetic chemists have come a long way in terms of the complexity of the target molecules they can reach. Progress was at first steady, but became rather dramatic in the second half of the 20th century. Vitamin B₁₂, ginkgolide B, calicheamicin γ_1^I , taxol, palytoxin, and brevetoxin B (Figure 3) are arguably six of the most impressive molecules to be synthesized to date.

Such accomplishments prompt comments such as “given enough manpower and money, synthetic chemists can make any complex molecule”; with such statements, attempts are made to criticize research in this field by declaring it mature and even dead! How unwise these statements are, for one only has to compare our synthetic power with that of nature in order to recognize the rather primitive state of the art. One message is clear: more expedient and economical processes are still needed to construct complex molecules, and this status will not change for some time to come. Asymmetric synthesis and catalysis are frontiers of enormous potential. Natural products provide wonderful opportunities for the development of new synthetic technologies and strategies for chemical synthesis. The following quotations from three masters of the science of inventing new reactions are appropriate here.

“When we have been faced with a problem of effecting a chemical synthesis we have sought known methods. We have not paused to think why we do not invent a new method every time. If we adopt this philosophy we are going to be extremely busy till the end of the century (a) trying to equal the enzymes, and (b) thinking of new ways of synthesis.”

Sir Derek H. R. Barton²⁰

“I believe that, for those who seek to discover new reactions, the most insightful lessons come from trying to trace important reactivity principles back to their origins.”

K. B. Sharpless²¹

“In defining strategies and reactions to construct complex molecules we require synthetic methods that can (i) perform a wanted structural change and none other (that is be chemoselective), (ii) orient the reacting partners in a correct fashion (be regioselective), (iii) create the correct orientations of the various parts of the molecule with respect to each other (be diastereoselective), and (iv) enable the formation of a molecule of one handedness or a mirror image isomer (be enantioselective). Such extraordinary demands are exciting challenges.”

B. M. Trost²²

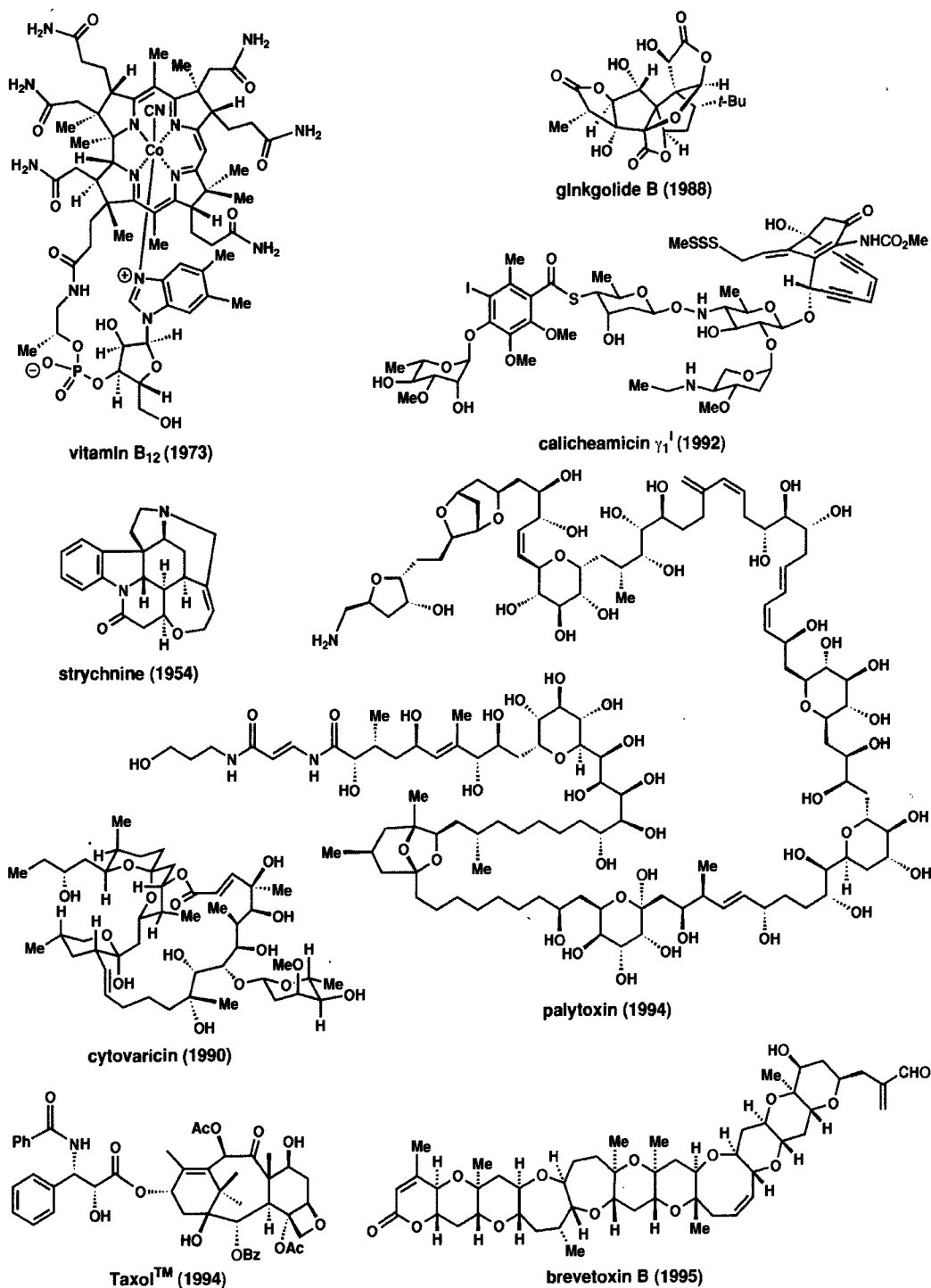


Figure 3. Some of the most complex natural products synthesized to date.

Nonetheless, the standards and expectations for a total synthesis are different today than they were years ago, and an important new era for this field seems to be on the horizon. Thus, today we witness novel natural products providing unique opportunities for the development of new synthetic strategies and new synthetic technologies, and associated programs of molecular design, chemical synthesis, and biological investigation of synthetic molecules related to the natural products at hand. The interface of the chemistry and biology of natural products with chemical synthesis as the bridging tool between the two disciplines provides a major new area of research. Medicine will no doubt be a major beneficiary of this practice.

1.7 Designed Molecules as Synthetic Targets



J.-M. Lehn

"This opens wide the door to the creative imagination of the chemist at the meeting point of chemistry with biology and physics, in order not only to discover but above all to invent, to create: the score of chemistry is not just to be played but to be composed!"

The essence of chemical science thus finds its full expression in the words of Leonardo da Vinci: 'Where nature finishes producing its own species, man begins, using natural things and in harmony with this very nature, to create an infinity of species.'"

J.-M. Lehn²³

The heart and the beauty of chemistry lies in its creative nature. On the basis of simple structural principles, the organic chemist is free to imagine and design unlimited numbers of new molecules never seen before either in nature or in the laboratory. This molecular design process is often guided by the particular interests of the chemist and can be aided by computer or manual molecular modeling studies. Depending on the area, the designed molecules can be of theoretical, physical, materials science, or biological interest.

These designed molecules then become potential targets for the synthetic chemist, and although some may look deceptively simple, they regularly present formidable challenges. Examples of designed molecules of theoretical interest (which may eventually attract a more practical interest depending on their properties) that have been synthesized in the laboratory are: tetrahedrane, prismane, cubane, dodecahedrane, [18]-annulene, heptahelicene, and various other aesthetically pleasing molecular constructs. Undoubtedly, however, the most fertile area of molecular design for the organic chemist is that of biologically interesting molecules. The fascination of biological action and of how living systems work, coupled with the potential for biomedical breakthroughs has prompted an avalanche of molecular design in academia and in the pharmaceuti-

cal industry, a trend that is continuously aided by the isolation and structural elucidation of both new biological receptors and of novel biologically active natural products. Frequently, the new molecular designs are based on the structures of bioactive natural products, or simply on principles of organic chemistry. It is thus hoped that their structure and chemical reactivity is translated into a specific biological action. Chemical synthesis followed by biological evaluation may then confirm or disprove the design hypothesis thus leading to useful information for further studies. Today, the interplay of molecular design, chemical synthesis, and biological evaluation is a powerful multidisciplinary approach to research at the chemistry-biology interface and to drug discovery and development. Numerous clinically useful drugs were discovered through this approach, including antibiotics, antiulcer drugs, and anticancer agents. Molecules for molecular recognition studies also fall into the category of designed molecules. They include cryptands, spherands, self-replicating systems, self-assembling systems, DNA-binding molecules, nanotubes, and artificial molecular receptors.

Combinatorial chemistry, a new chapter of organic synthesis, is now developing rapidly. This new approach to synthesizing large designed or random chemical libraries through application of solid phase synthetic methods, promises to revolutionize the process of drug discovery in the pharmaceutical industry.²⁴

1.8 Synthetic Strategy

Faced with a target molecule, how does a synthetic chemist go about devising a synthetic plan for its construction? For a chemist considering a complex molecule containing many sensitive functional groups, rings, elements of stereochemistry, and unusual bond connectivities, this question presents a challenge requiring logical analysis and intellectual input of the highest order. In the early days of the science, when relatively simple targets were considered, the chemist would try to connect potential starting materials with the target molecule by known reactions. The starting materials were often closely related to the final products. As the target molecules became more complex, this process became impractical. Higher levels of intellectual planning and skill in execution were demanded. Synthetic chemists rose to the challenge by devising a new armory of methods and novel strategies. As the field of total synthesis developed and its intellectual demands were recognized, the science was received with much excitement and euphoria. The contributions of R. B. Woodward and the developments in the electronic theory and mechanisms of organic reactions, conformational analysis, analytical and chromatographic techniques, crystallographic and spectroscopic methods, and new synthetic technology that took place after World War II greatly facilitated this outburst of

activity in the field and placed synthesis on center stage. As a strategist, the synthetic chemist quickly became a master of the art with formidable targets falling one after the other, and each new accomplishment pushing the envelope further and further in terms of complexity and efficiency. Landmark syntheses such as strychnine (Woodward, 1954),²⁵ reserpine (Woodward, 1956),²⁶ penicillin V (Sheehan, 1957),²⁷ colchicine (Eschenmoser, 1959),²⁸ and chlorophyll (Woodward, 1960)²⁹ are monuments to the ingenuity and character of the chemists of this era. Thinking about synthetic strategy, however brilliant as it was, was not formulated into a systematic and universal approach until E. J. Corey introduced retrosynthetic analysis in the 1960s.

1.9 Retrosynthetic Analysis

“Retrosynthetic (or antithetic) analysis is a problem-solving technique for transforming the structure of a synthetic target (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. The transformation of a molecule to a synthetic precursor is accomplished by the application of a transform, the exact reverse of a synthetic reaction, to a target structure. Each structure derived antithetically from a TGT then itself becomes a TGT for further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structures as nodes and pathways from bottom to top corresponding to possible synthetic routes to the TGT.”

E. J. Corey³⁰

With these words, E. J. Corey defines for us the concept of retrosynthetic analysis for which he received the Nobel Prize in chemistry in 1990. Nowadays, it has become routine to think about a target molecule in terms of its retrosynthetic analysis. Furthermore, it is hard to imagine how chemists developed synthetic strategies prior to the formulation of these concepts in the 1960s, without thinking, at least subconsciously, in these terms about complex organic structures.

Typically the synthetic strategist when faced with a new challenge focuses on the target, pondering and analyzing the proposed structure and identifying strategic bonds that may be advantageously disconnected in the retrosynthetic sense. Several such bonds and disconnections may become apparent either as a sequence to simplify the structure, or as alternative approaches to such simplification. In a parallel mental process, the synthetic chemist also asks and attempts to answer the question of how to construct, in the synthetic direction, each bond broken by retro-

synthesis, and how, if possible at all, to convert the simpler intermediates so generated to the more advanced targets in the retrosynthetic scheme. This can be an exhilarating experience, particularly at moments of brilliant flashes of inspiration, as perceived, of course, by the practitioner. The key to success at this stage is to be quite thorough and to uncover subtle features of the structure under consideration that may lead to elegant and efficient synthetic schemes. Hastiness and compromise have no place in such planning and should be avoided. Instead, forcing oneself to upgrade and refine the retrosynthetic analysis, always aiming to apply novel disconnections and unprecedented maneuvers, frequently proves rewarding.

Having exhausted all retrosynthetic possibilities, the strategist is then in a position to evaluate the possible paths uncovered and devise the most attractive synthetic strategy for the construction of the target molecule. The strategy may dictate the invention of new reactions, reagents, and tactics, and may require model studies before synthesis of the real target can start. This is usually a good practice, for it is destined, more often than not, to result in new synthetic technology, a vital feature of a novel total synthesis, and to pave the way for a projected total synthesis. Other attractive features of a planned synthetic strategy are: (a) efficient synthetic reactions; (b) brevity; (c) readily available and inexpensive starting materials; (d) practical and convenient conditions; (e) flexibility of modification in case of pitfalls; (f) adaptability to the synthesis of other members of the structural family, be they naturally occurring or designed molecules; and (g) novelty, elegance, and artistry!

It is of paramount importance to recognize that in total synthesis the achievement itself is not always the prize or the most significant advance. Rather, it is the journey towards the target molecule that becomes the essence and significance of the exercise. The invention and development of new synthetic technology and strategies, and the molecular design, chemical synthesis, and biological investigation of bioactive compounds structurally related to the target are two emerging and important aspects of modern total synthesis. Chemists and biologists will no doubt be busy for a long time harvesting the benefits of this newly emerging field of investigation that combines the best of chemistry and biology.

The following quotes from R. B. Woodward and C. P. Cavafy, a contemporary Greek poet, amplify the real essence of total synthesis in a chemical and more general sense, respectively.

"Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective."

R. B. Woodward³¹

Ithaca

*When you start on your journey to Ithaca,
Then pray that the road is long,
Full of adventure, full of knowledge,
Do not fear the Lestrygonians
And the Cyclopes and the angry Poseidon.
You will never meet such as these on your path,
If your thoughts remain lofty, if a fine
Emotion touches your body and your spirit.
You will never meet the Lestrygonians,
The Cyclopes and the fierce Poseidon,
If you do not carry them within your soul,
If your soul does not raise them up before you.*

*Then pray the road is long.
That the summer mornings are many,
That you will enter ports seen for the first time
With such pleasure, with such joy!
Stop at Phoenician markets,
And purchase fine merchandise,
Mother-of-pearl and corals, amber and ebony,
And pleasurable perfumes of all kinds,
Buy as many pleasurable perfumes as you can;
Visit hosts of Egyptian cities,
To learn and learn from those who have knowledge.
Always keep Ithaca fixed in your mind.
To arrive there is your ultimate goal.
But do not hurry the voyage at all.
It is better to let it last for long years;
And even to anchor at the isle when you are old,
Rich withal that you have gained on the way,
Not expecting that Ithaca will offer you riches.*

*Ithaca has given you the beautiful voyage.
Without her you would never have taken the road.
But she has nothing more to give you.*

*And if you find her poor, Ithaca has not defrauded you.
With the Great Wisdom you have gained, with so much experience,
You must surely have understood by then what Ithacas mean.*

C. P. Cavafy³²



C. P. Cavafy

1.10 *Classics in Total Synthesis*

One of the most difficult tasks we faced in writing this book was the selection of what we considered to be “classics” in the art of total synthesis, particularly under the pressure of space and time. With so much wealth and so many brilliant accomplishments it was hard to come to the inevitable close. We sincerely apologize to those whose elegant work could not be included owing to the limitations of this undertaking; and we can offer the hope, that in the event of a second volume, their masterpieces will be there. The chosen syntheses represent both the Woodward and Corey eras, and project into the future in terms of the new criteria for target selection and expectations of the exercises. Each following chapter in this book describes a total synthesis of a natural product and is divided into the following sections: Introduction, Retrosynthetic Analysis and Strategy, Total Synthesis, and Conclusion; references are given separately in each chapter. Even though the natural products discussed are structurally distinct, the discussions of their syntheses revolve around similar themes: natural origin and biological activity of the molecules, the concept of retrosynthetic analysis and the evolution of the synthetic strategy, important synthetic reactions and reagents, mechanistic concepts behind the reactions and stereoselectivities, and conclusions drawn from the experience of the syntheses are all presented in a unified approach. This presentation style reflects not only today’s systematic approach to total synthesis but also facilitates understanding of the basic principles involved in the synthesis of complex molecules. It is hoped that this approach will well serve those who wish to pursue the art of total synthesis and those who are destined to go beyond the boundaries set by the examples included in this book.

An important objective of our undertaking was identifying and projecting the important synthetic reactions in each total synthesis discussed. Thus, considerable space has been devoted to presenting and analyzing important methodology. Amongst the reactions and concepts discussed are: the Woodward–Hoffmann rules, the cation- π cyclization, the Diels–Alder reaction, the intramolecular nitron and nitrile oxide/olefin cyclization, the Cope, oxy-Cope, aza-Cope, and Claisen [3,3] sigmatropic rearrangements, radicals in organic synthesis, the cobalt-mediated cyclization of acetylenic compounds, macrolactonization reactions, Wittig and Horner–Wadsworth–Emmons reactions, the Evans aldol reaction, chelation-controlled carbonyl addition reactions, the Sharpless asymmetric epoxidation and asymmetric dihydroxylation reactions, other catalytic asymmetric reactions, the Bergman cycloaromatization reaction of conjugated enediyne, the McMurry and Shapiro reactions, the Stille and related palladium-catalyzed C–C bond forming reactions, the hydroxyepoxide-opening reactions for cyclic ether formation, [2+2] photo- and thermal cycloadditions, $\text{NiCl}_2/\text{CrCl}_2$ -mediated C–C bond forming reaction, the bridging of macrocycles to bicycles, glycoside bond forming reactions, and a variety of novel cascade sequences and rearrangement reactions.

It should be emphasized that, for pedagogic purposes and in order to avoid long discussions and possible confusion, the Retrosynthetic Analysis and Strategy sections do not always present the original analysis and thoughts of the synthetic strategists involved. Rather, the final plan for the total synthesis is used to illustrate the retrosynthetic analysis. On occasion, mechanistic interpretations are offered, which are not found in the original papers and are, therefore, speculations on our part. These are solely our responsibility, and we apologize in advance to the original authors for any misinterpretations of their results.

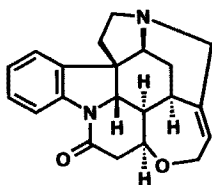
We will now begin our journey in total synthesis from the 1950s to the 1990s. As you read through these pages we hope your journey to "Ithaca" will be as adventurous, educational, and enjoyable as was our odyssey of putting together this book on "Classics in Total Synthesis".

This forty-year exposition of the state of the art should serve to put total synthesis in perspective as the 20th century draws to a close.

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1: strychnine

R. B. Woodward (1954)

Strychnine

2.1 Introduction

The *Strychnos* species, indigenous to the rain forests of the South-east Asian archipelagos and the Coromandel Coast of India, harbor the notorious poison strychnine (**1**). The poisonous properties of the *Strychnos* species were recognized in Europe as early as the sixteenth century, and in 1818 Pelletier and Caventou reported the isolation of strychnine, in pure form, from the beans of *Strychnos ignatii*.¹ Before the advent of modern spectroscopic techniques and due principally to the independent and brilliant researches of Sir Robert Robinson and Herman Leuchs, a forty-year period of extensive study culminated in the elucidation of strychnine's structure in 1946.² In the early 1950s, two independent X-ray crystallographic investigations confirmed the gross structure of strychnine,³ and in 1956 X-ray crystallographic results revealed that the absolute configuration of strychnine is that shown in structure **1**.⁴

Strychnine, the most celebrated member of the *Strychnos* alkaloids, possesses a complex polycyclic structure which is assembled from only twenty-four skeletal atoms. In addition to its obvious architectural complexity, strychnine's structure contains a contiguous array of six unsymmetrically substituted tetrahedral (asymmetric) carbon atoms of which five are included within one saturated six-membered ring. The intimidating structure of the strychnine molecule elicited the following remark by Sir Robert Robinson in 1952: "For its molecular size it is the most complex substance known."⁵

The strychnine molecule presented an unparalleled challenge to anyone interested and skilled in the art of constructing complex molecules in the 1950s. The establishment of strychnine's exceed-

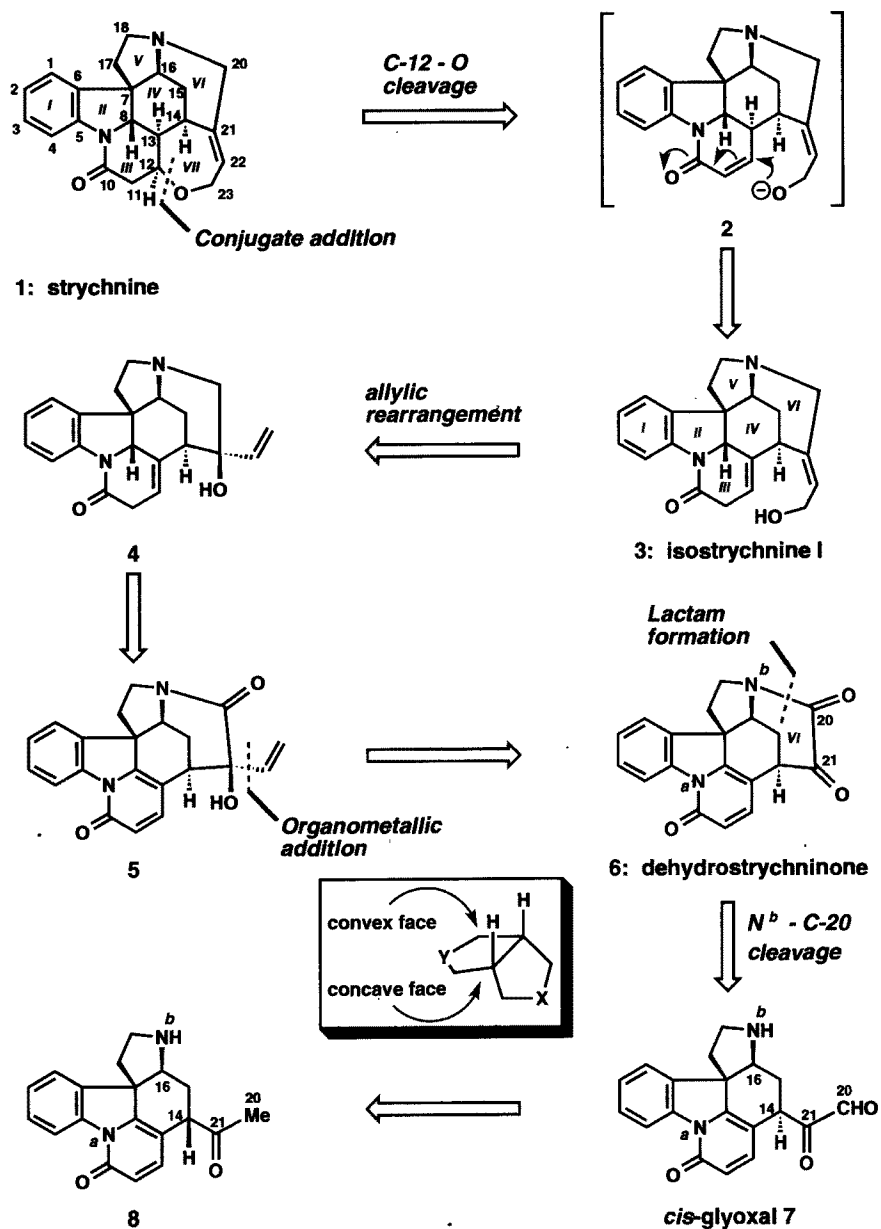
ingly complex structure through chemical degradation is an outstanding achievement of classical structural chemistry which is equalled by the landmark chemical synthesis of strychnine by R. B. Woodward and his colleagues at Harvard.⁶ Only eight years intervened between the disclosure of strychnine's structure in 1946 and the first chemical synthesis of this substance by Woodward *et al.*⁷ The employment of only the simplest of reagents to carry out impressive structural transformations is perhaps the most distinguishing feature of Woodward's elegant and instructive strychnine synthesis.

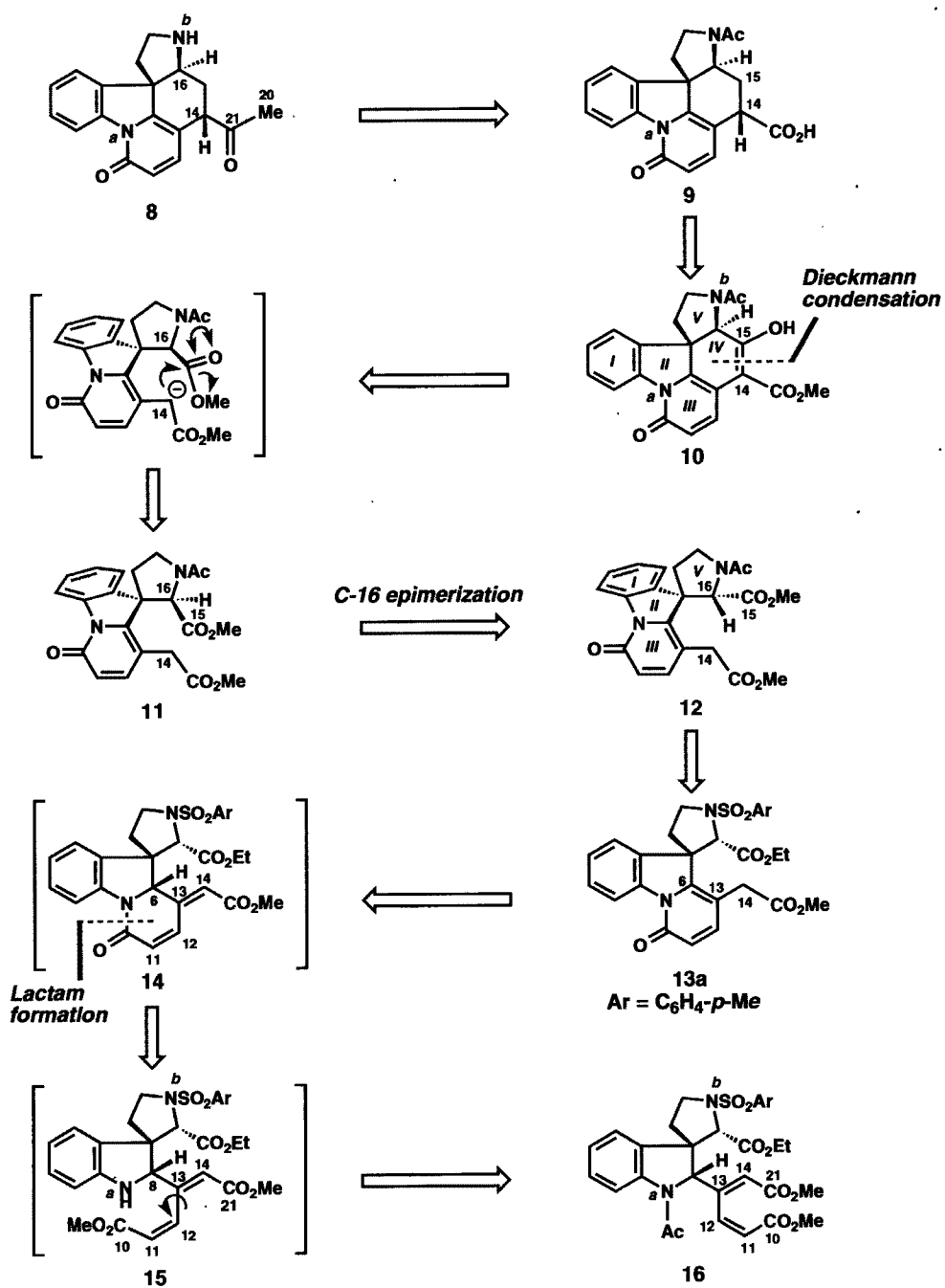
2.2 Retrosynthetic Analysis and Strategy

The general features of Woodward's strychnine synthesis are outlined retrosynthetically in Scheme 1. It was known at the time that isostrychnine I (**3**), a strychnine degradation product, could be reconverted to strychnine in a single step. In the synthetic direction, the action of potassium hydroxide on **3** induces its conversion to the corresponding α,β -unsaturated isomer (**2**) with concomitant creation of the stereogenic center at C-13. Once formed, intermediate **2** can either revert back to isostrychnine I or it can participate in an intramolecular Michael addition reaction to give strychnine. With this precedent in hand, it was logical to defer the assembly of the seven-membered ether ring to the last stage in the synthesis. The synthetic objective now becomes isostrychnine I (**3**), and it was anticipated that this substance could be derived from intermediate **4** through a straightforward isomerization or allylic rearrangement reaction. Removal of the vinyl appendage from intermediate **5**, the projected precursor of **4**, furnishes dehydrostrychnine (**6**). With adjacent carbonyl groups at positions 20 and 21, intermediate **6** would be expected to react readily with nucleophilic species at C-21. Moreover, the two diastereotopic faces of the C-21 ketone carbonyl are significantly different, and a nucleophilic attack on the C-21 ketone carbonyl should proceed in a highly diastereoselective manner from the much less hindered convex face of **6** (see insert, Scheme 1).

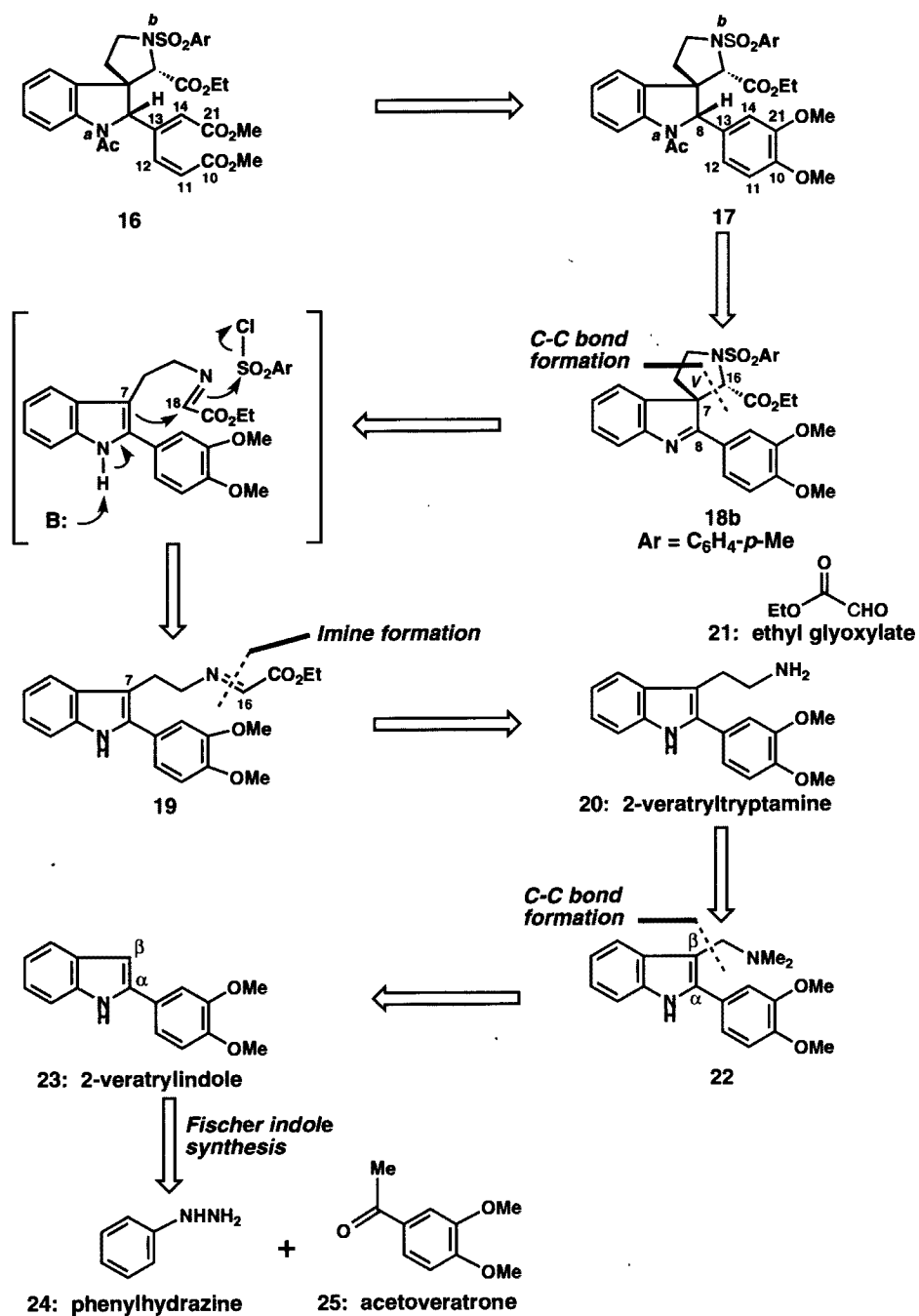
Retrosynthetic simplification of intermediate **6** is rather straightforward, furnishing *cis*-glyoxal **7** as a potential precursor. In the forward sense, an attack of N^b upon the C-20 aldehyde carbonyl could occur to give ring VI of strychnine in the form of a cyclic hemiaminal which can then undergo oxidation to **6**. *cis*-Glyoxal **7** could be formed through oxidation of methyl ketone **8**, followed by epimerization at C-14. Through some straightforward functional group manipulations, amino ketone **8** could conceivably be derived from carboxylic acid **9**.

Although "retrosynthetic simplification" of intermediate **9** introduces functionality and would appear to complicate matters, retro-

**Scheme 1.** Retrosynthetic analysis of strychnine (1).

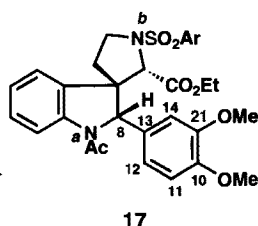
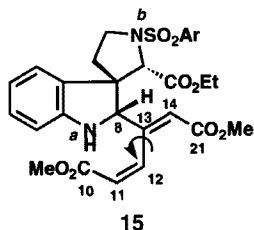


Scheme 1. Retrosynthetic analysis of strychnine (1) (continued).



Scheme 1. Retrosynthetic analysis of strychnine (1) (continued).

synthetic cleavage of the indicated bond in **10** disassembles ring IV and achieves significant structural simplification. It was anticipated that intermediate **10** could be derived from diester **12** through a Dieckmann condensation.⁸ Thus, in the synthetic direction, exposure of **12** to a competent base could conceivably induce epimerization at C-16 to give epimer **11**. Deprotonation at position 14 would then afford an ester enolate anion which would find itself in spatial proximity to the electrophilic C-15 methyl ester group. In such a favorable setting, the crucial Dieckmann condensation (see arrows) should proceed with reasonable facility to give, after expulsion of a molecule of methanol and keto-enol tautomerization, intermediate **10**.



Intermediate **13a**, a potential precursor of intermediate **12**, could be fashioned in a single step from intermediate **16**. Under conditions suitable for the removal of the acetate grouping from N^a, it seems likely that spontaneous lactamization would also occur (see intermediate **15**) to give aromatic pyridone **13a**, after isomerization of **14**. The intramolecular attack upon the C-10 carbomethoxyl group by N^a in **15** is a process that ought to be facilitated by the *cis* Δ^{11,12} double bond. Intramolecular attack of N^a on the C-21 carbomethoxyl group is prohibited by the *trans* Δ^{13,14} double bond.

The recognition that the reactive array of atoms in **16** (see numbered atoms) could evolve from a very stable, substituted aromatic ring demonstrates great insight. It was anticipated that oxidative cleavage of the electron-rich veratryl ring in intermediate **17** between positions 10 and 21 (strychnine numbering) would afford diester **16**. Thus, in only two synthetic steps, it is conceivable that **17** could be transformed into **13a**, a molecule that possesses rings I, II, III, and V of strychnine and functionality suitable for the elaboration of ring IV. Retrosynthetic cleavage of the C7-C16 bond in **18b**, the retrosynthetic precursor of **17**, provides substituted indole **19** as a potential precursor. With nucleophilic character at C-7 and electrophilic character at C-16, it is conceivable that the action of pyridine and *para*-toluenesulfonyl chloride on **19** would lead to the formation of ring V (see arrows). Intermediate **19** is simply a Schiff base and it could be derived in one step from the reaction of 2-veratryltryptamine (**20**) with ethyl glyoxylate (**21**). Intermediate **20** could, in turn, be fashioned through homologation of intermediate **22**.

During the planning stages, the aromatic veratryl ring was expected to serve two important roles in the synthesis. Not only would it serve as a stable precursor for the reactive, unsaturated bismethyl ester moiety in intermediate **16**, but it would also guide the functionalization of the indole nucleus in **23**. The veratryl ring, appended as it is to the α position in 2-veratrylindole (**23**), should direct the attack of an electrophilic species upon the electron rich indole nucleus to the β position. The aromatic veratryl ring in **23** thus serves as a masking group for the inherently reactive indole α carbon and yet it could conceivably be modified, at some later

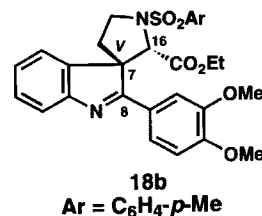
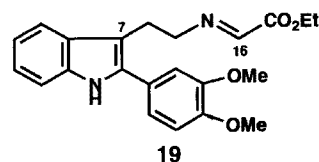
stage, in a manner that will permit the elaboration of rings III, IV, and VI of strychnine. 2-Veratrylindole (**23**) thus provides a logical starting point for the synthesis and it could be prepared from simple building blocks (intermediates **24** and **25**) through a Fischer indole synthesis.⁹

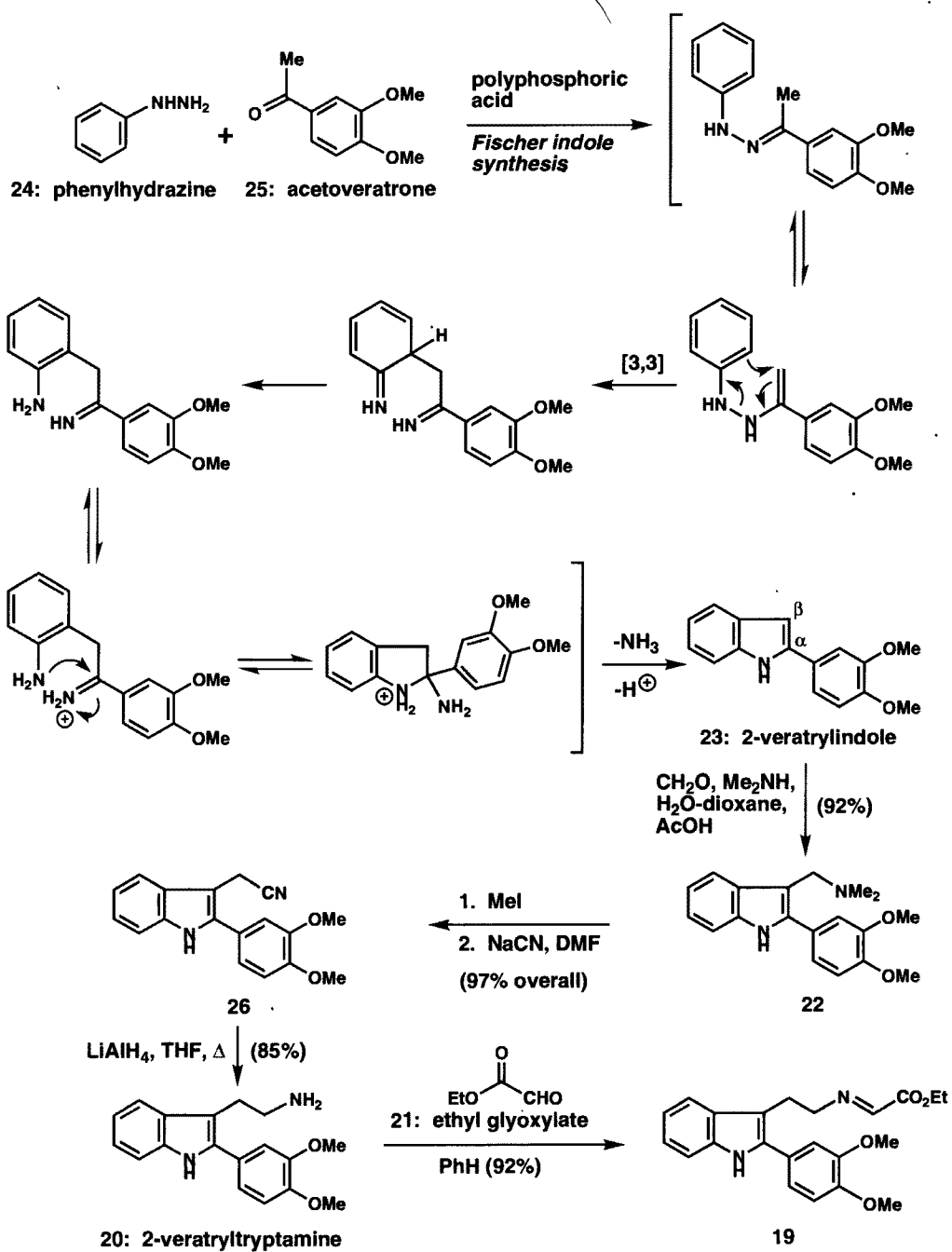
2.3 Total Synthesis

Woodward's strychnine synthesis commences with a Fischer indole synthesis using phenylhydrazine (**24**) and acetoveratrone (**25**) as starting materials (see Scheme 2). In the presence of polyphosphoric acid, intermediates **24** and **25** combine to afford 2-veratrylindole (**23**) through the reaction processes illustrated in Scheme 2. With its α position suitably masked, 2-veratrylindole (**23**) reacts smoothly at the β position with the Schiff base derived from the action of dimethylamine on formaldehyde to give intermediate **22** in 92% yield. *N*-Methylation of the dimethylamino substituent in **22** with methyl iodide, followed by exposure of the resultant quaternary ammonium iodide to sodium cyanide in DMF, provides nitrile **26** in an overall yield of 97%. Condensation of 2-veratryltryptamine (**20**), the product of a lithium aluminum hydride reduction of nitrile **26**, with ethyl glyoxylate (**21**) furnishes Schiff base **19** in a yield of 92%.

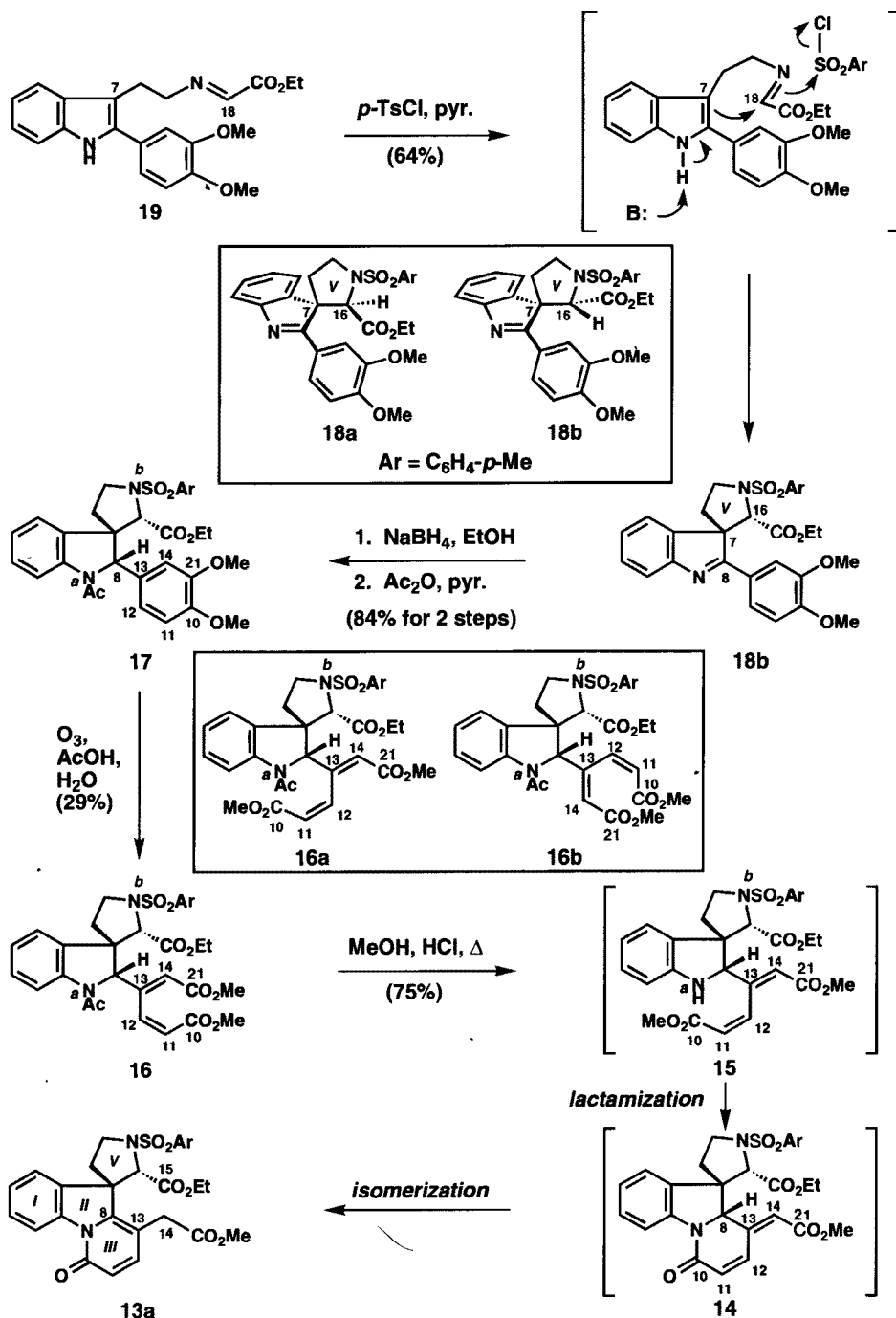
Having witnessed the expedient synthesis of intermediate **19**, we are now in a position to address the construction of strychnine's ring V (see Scheme 3). It is interesting to note that only three atoms intervene between the nucleophilic indole β -carbon (C-7) and the electrophilic C-16 position. A close spatial relationship between sites that have complementary reactivity would normally favor a pathway leading to their union. In the event, treatment of **19** with pyridine and *para*-toluenesulfonyl chloride induces a smooth cyclization reaction to give the spiroannulated molecule, intermediate **18b** (see arrows), as the only product in 64% yield. Although an examination of models of **18a** and **18b** certainly did not reveal a strong preference for either C-16 epimer, it seemed likely, on steric grounds, that the reaction pathway leading to **18b** would be favored. Reduction of indolenine **18b** with sodium borohydride, followed by acetylation, provides intermediate **17** in an overall yield of 84%. The newly created stereogenic center at C-8 in **17** most likely possesses the configuration shown, since attack by borohydride ion is most likely to occur from the more accessible face of trigonal C-8 in **18b**. Ultimately, however, it is of no consequence which C-8 epimer of **17** is formed because the C-8 stereocenter is destroyed at a later stage in the synthesis.

In the early stages of the synthesis, the stable, aromatic veratryl group had served admirably as a masking device for the α -carbon of the indole nucleus. It permitted the processes leading to the for-

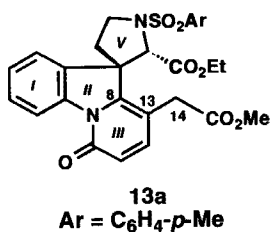
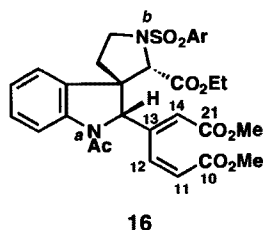
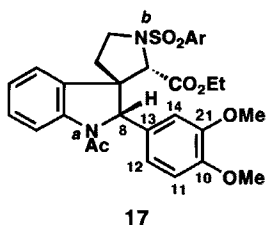




Scheme 2. Synthesis of intermediate 19.



Scheme 3. Synthesis of intermediate 13a.

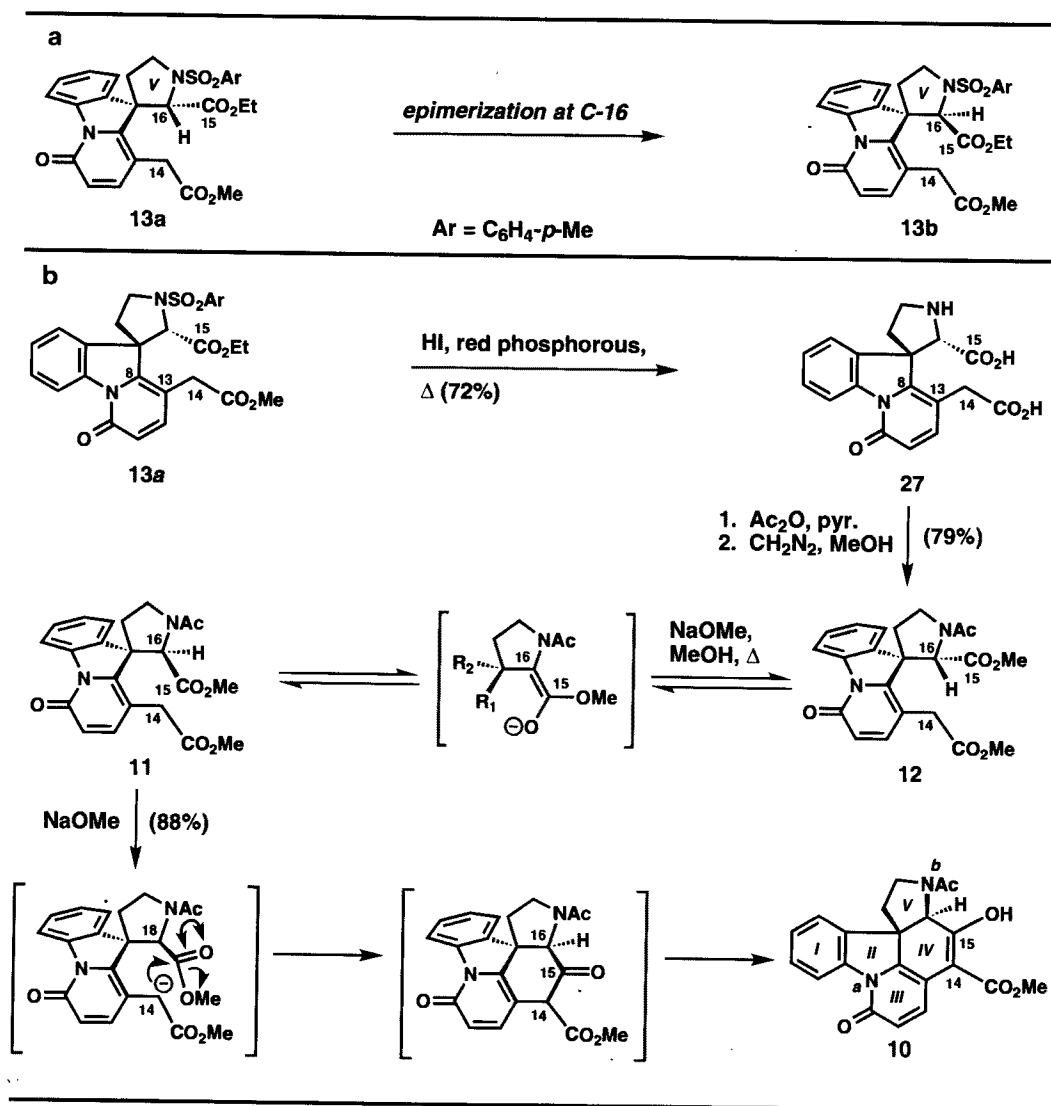


mation of ring V of strychnine to proceed without incident, and it was tolerant of the reaction conditions to which it was subjected. Although the veratryl group is just one of three aromatic rings in intermediate **17**, the Woodward group anticipated at the outset that the veratryl group could be modified in a selective and productive fashion at some stage in the synthesis. In particular, the veratryl group, substituted as it is with two methoxyl groups, is appreciably more electron rich than the other two aromatic rings and it should, therefore, be possible to modify selectively the veratryl ring with some electron-deficient reagent. In the event, when **17** is subjected to ozone in aqueous acetic acid, the site of unsaturation flanked by the two electron-donating methoxyl groups is oxidatively cleaved in a completely selective manner to give ester **16**.

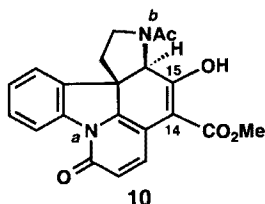
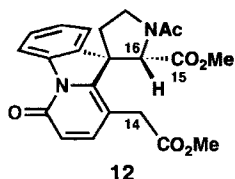
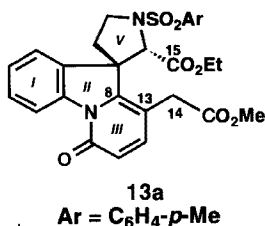
With its veratryl ring cleaved, intermediate **16** enjoys even greater rotational freedom than its predecessor **17**. With free rotation about the C12-C13 bond, it is entirely possible that cleavage of the acetyl group affixed to N^a would be followed by an intramolecular attack by N^a upon the C-10 carbomethoxyl group six atoms away. This lactamization process would culminate in the formation of ring III of strychnine and would likely benefit from the *cis* C11-C12 double bond (see **16a**). It is important to note that a similar cyclization involving the C-21 carbomethoxyl group is precluded by the *trans* C13-C14 double bond (see **16b**).

Provided that such a cyclization reaction could be brought about, it is important to note that the initially formed six-membered lactam (see **14** in Scheme 1) would be unstable with respect to its aromatic isomer **13a**. A straightforward olefin isomerization reaction would accomplish the conversion of **14** to **13a**. Of course, a prerequisite for the sequence of reactions just outlined is cleavage of the acetyl group at N^a, and it was very gratifying to observe that the desired cleavage could be brought about with boiling methanolic hydrogen chloride to give, after lactamization and olefin isomerization, intermediate **13a** in 75% yield. In one step, all three transformations take place smoothly. It is interesting to note that transesterification of the C-15 ethyl ester does not occur under these rather vigorous conditions.

All of the processes that we have addressed thus far have proceeded smoothly and have resulted in the synthesis of intermediate **13a**, a tetracyclic molecule which is adorned with functionality that could permit the construction of ring IV of strychnine. With an activated methylene group at position 14 and an electrophilic ester carbonyl at position 15, intermediate **13a** would appear to be a viable substrate for a Dieckmann condensation.⁸ It is, however, important to recognize that the two groups between which a bond must be formed are oriented on opposite sides of the molecular plane defined by ring V in intermediate **13a**, a circumstance which prohibits the desired Dieckmann condensation. Thus, a prerequisite for the desired bond-forming event is inversion of the stereogenic center at C-16 to give the epimer **13b** (Scheme 4a). In **13b**, the activated methylene at C-14 and the electrophilic C-15 ester carbonyl



Scheme 4. Epimerization of intermediate **13a** (a) and synthesis of intermediate **10** (b).

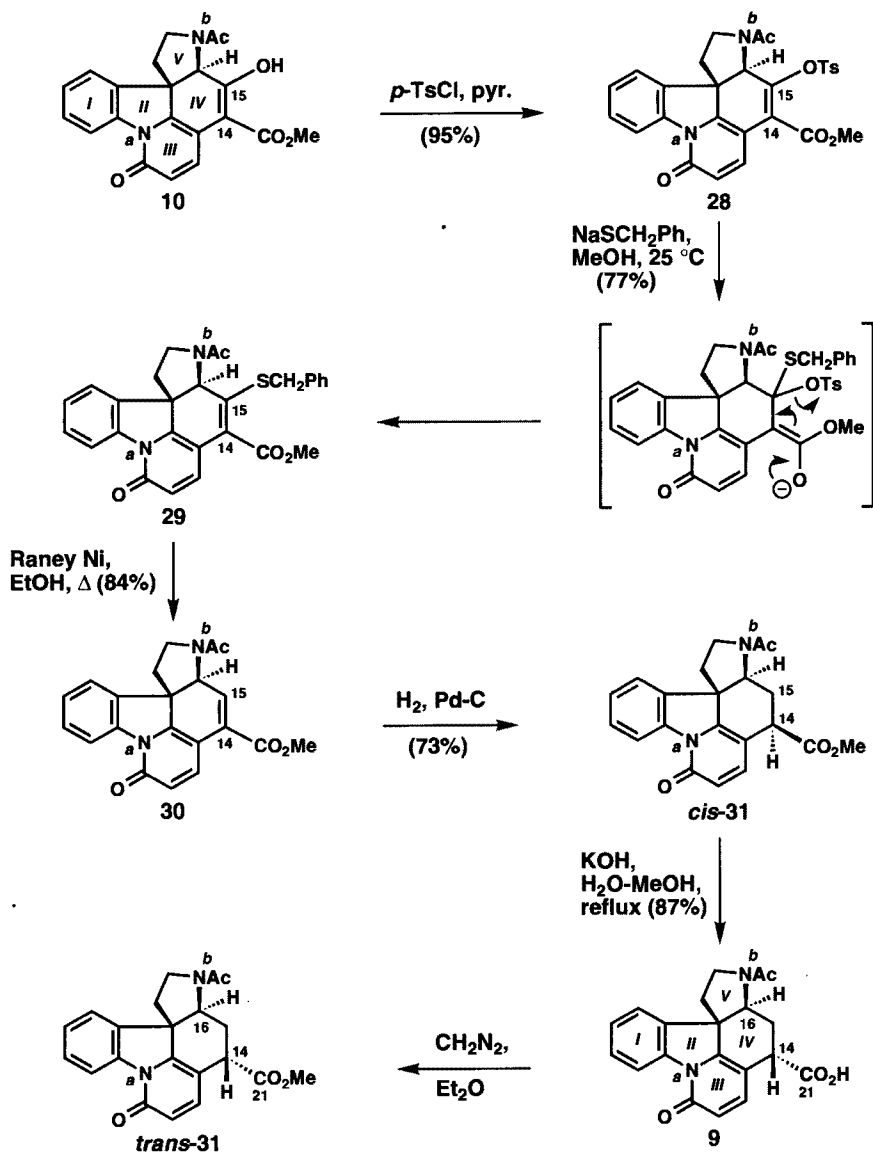


occupy proximal regions of space and the prospects for achieving the formation of a bond between these two groups through a Dieckmann condensation seem excellent.

Woodward actually anticipated all along that the ethoxycarbonyl group at position 15, the electrophile in the projected Dieckmann condensation, could, through a base-induced epimerization reaction, allow such an inversion to take place. However, it was not anticipated that exposure of **13a** to a base would result in destruction of the carefully constructed ring V! In the presence of sodium methoxide, intermediate **13a** suffers ready β -elimination of the stable toluene sulfonate anion, an event that is followed by a sequence of other destructive processes. It was thus necessary to remove the offending toluenesulfonyl group prior to the Dieckmann condensation. Treatment of **13a** with hot hydriodic acid and red phosphorous results in removal of the toluenesulfonyl group and hydrolysis of both the methyl and ethyl ester moieties of **13a** to give diacid **27** in 72 % yield (see Scheme 4b). Subjection of **27** to sequential acetylation and esterification reactions then provides *N*-acetyl dimethyl ester **12** in an overall yield of 79 %.

In its present form, intermediate **12** is not a viable substrate for the crucial Dieckmann condensation; it must undergo prior epimerization at C-16. When intermediate **12** is treated with sodium methoxide in hot methanol, enolization at C-16 occurs and an equilibrium is established between **12** and a diastereomeric substance, intermediate **11**. Once formed, **11** can either revert back to **12** through the planar enolate form, or it can participate in a productive cyclization reaction to give a new six-membered ring. Under these conditions, the desired transformations take place with exceptional facility to give, after acidification of the reaction medium, enol ester **10**.

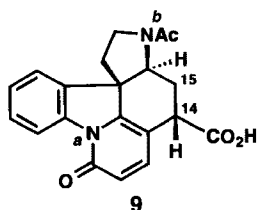
Enol ester **10** was found to be a very stable substance with respect to its keto ester tautomer, and it produced a distinctive UV spectrum. The stability of enol ester **10** is likely a consequence of the electron-withdrawing pyridone ring, and it was gratifying to find that **10** could be smoothly transformed into enol tosylate **28** upon treatment with *para*-toluenesulfonyl chloride in pyridine (see Scheme 5). This particular transformation constitutes the first step of a straightforward sequence of reactions that accomplishes the necessary deoxygenation at C-15. When a solution of **28** in methanol is treated with sodium benzylmercaptide at room temperature, β -benzylmercaptoester **29** forms smoothly through a transformation that can be formulated as an addition/elimination reaction. That is to say, benzylmercaptide ion initiates the event by adding in a Michael fashion to unsaturated ester **28** to give an ester enolate which subsequently collapses with concomitant β -elimination of the toluenesulfonyloxy group. The final step in the C-15 deoxygenation sequence requires a reduction of the carbon-sulfur bond in **29**. This objective is achieved easily with deactivated Raney nickel in hot ethanol to give unsaturated ester **30**. Saturation of the electron-deficient $\Delta^{14,15}$ double bond in **30** with hydrogen in the presence of



Scheme 5. Synthesis of intermediate 9.

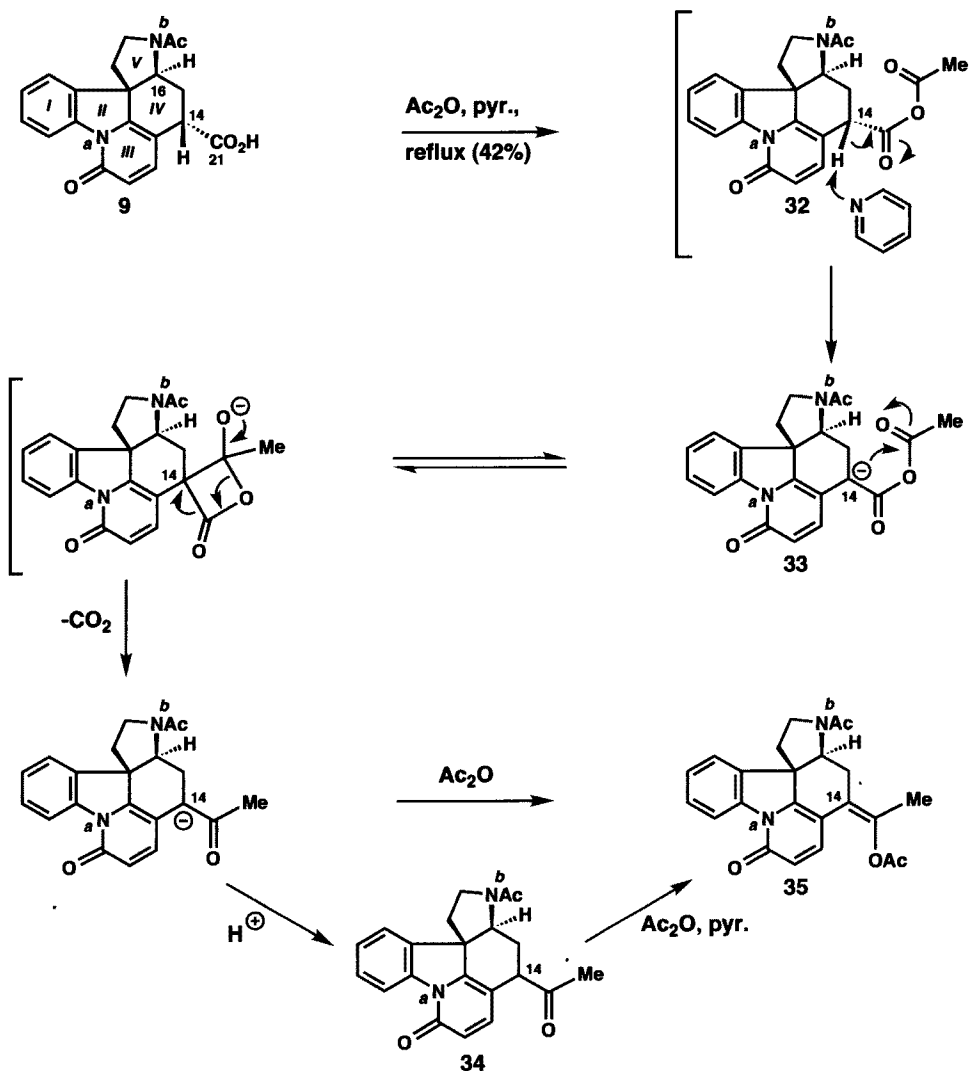
palladium on charcoal provides, as the major product, *cis* ester **31** and a small amount of the isomeric *trans* ester.

It is instructive to address an interesting stereochemical issue. The production of *cis*-**31** as the major diastereoisomer in the hydrogenation reaction is certainly not surprising; the biased framework of **30** enforces the addition of hydrogen to proceed across the much less hindered face of the $\Delta^{14,15}$ olefin to give *cis* ester **31**. But, nevertheless, *cis* ester **31**, with a crowded disposition of functionality, should be unstable relative to the corresponding *trans* ester (i.e. the C-14 epimer of **31**). Under conditions suitable for the saponification of the methyl ester in *cis*-**31**, it seems likely that epimerization at C-14 would also occur. Indeed, alkaline hydrolysis of *cis*-**31**, followed by treatment of the resultant carboxylic acid **9** with diazomethane, furnishes a methyl ester identical to the minor isomer formed in the hydrogenation of **30**. It was well known at the time that the hydrolysis of hindered, epimerizable esters, such as *cis*-**31**, is often preceded by inversion to the more stable and more readily hydrolyzed stereoisomer. Of course, the epimerization process proceeds through the intermediacy of an ester enolate and, in the context of **31**, removal of the C-14 methine hydrogen as a proton should be a facile process.



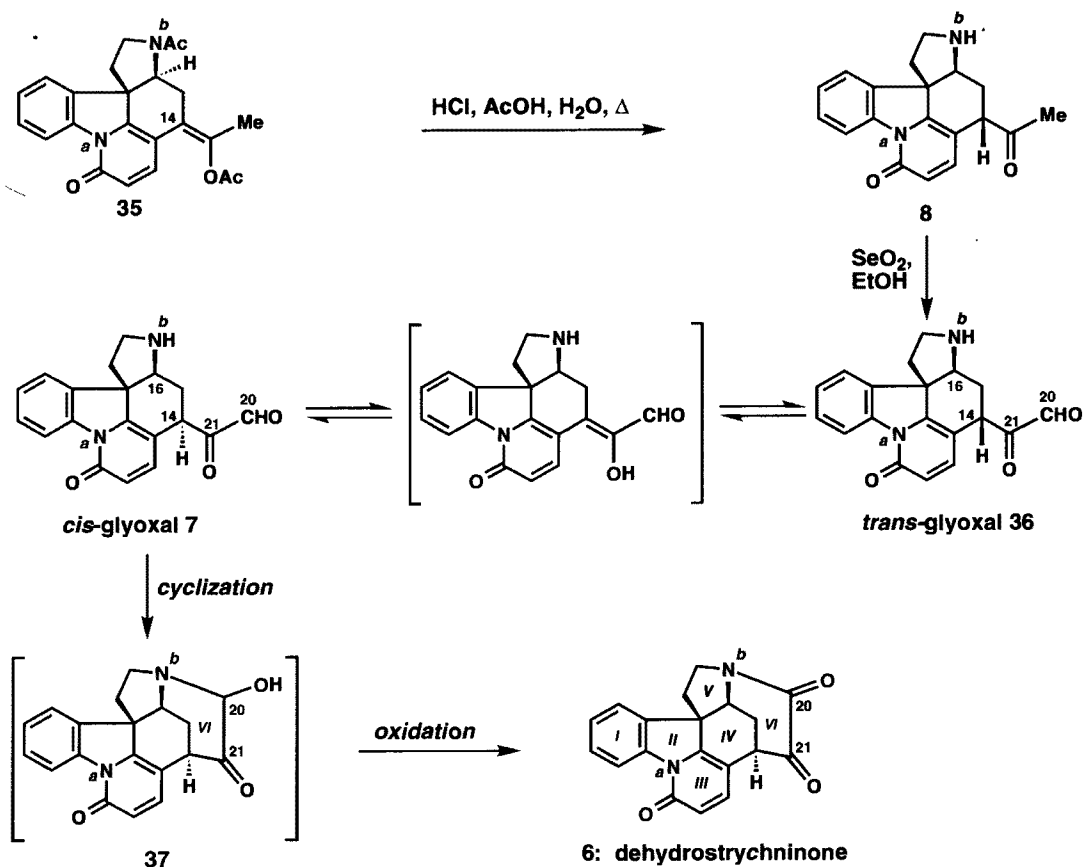
The processes that we have described thus far have culminated in the synthesis of racemic acid **9**, an intermediate which contains five of strychnine's seven rings. The same substance, albeit in enantiomerically pure form, was available through degradation of the strychnine molecule and it was possible, at this stage, to confirm that the preceding steps in the synthesis had taken the expected and desired course. In particular, the infrared spectrum of the racemic synthetic acid **9** and that of the derived methyl ester were identical to those of the corresponding enantiomerically pure compounds obtained through degradation of strychnine. It was also found that racemic acid **9** can be readily resolved with quinidine to give enantiomerically pure material which was identical in all respects to the corresponding substance in the natural series. A fortunate consequence of having access to optically pure carboxylic acid **9** through the synthetic sequence described above and through degradation of strychnine is that sufficient quantities of this key pentacyclic intermediate could be procured for further advancement.

With the C-16 nitrogen atom (N^b) and a carboxyl group four carbon atoms removed, intermediate **9** would appear to be well suited for the elaboration of ring VI of strychnine. The construction of ring VI would require inversion of the stereogenic center at C-14 and installation of a methylene bridge between N^b and C-21. Treatment of *N*-acetyl acid **9** with acetic anhydride and pyridine at reflux provides enol acetate **35** in 42% yield (see Scheme 6). This interesting transformation undoubtedly involves the initial formation of mixed anhydride **32**. Flanked by the electron-withdrawing pyridone ring and the C-21 carbonyl group, the C14-H bond is labile and, under these conditions, deprotonation can occur to give **33**. This

**Scheme 6.** Synthesis of intermediate 35.

species, containing as it does an enolate anion and an electrophilic carbonyl in spatial proximity, can then undergo conversion to methyl ketone **34** in the manner illustrated in Scheme 6. Finally, enolization of ketone **34**, followed by acetylation of the enolate oxygen atom with acetic anhydride, would give enol acetate **35**.

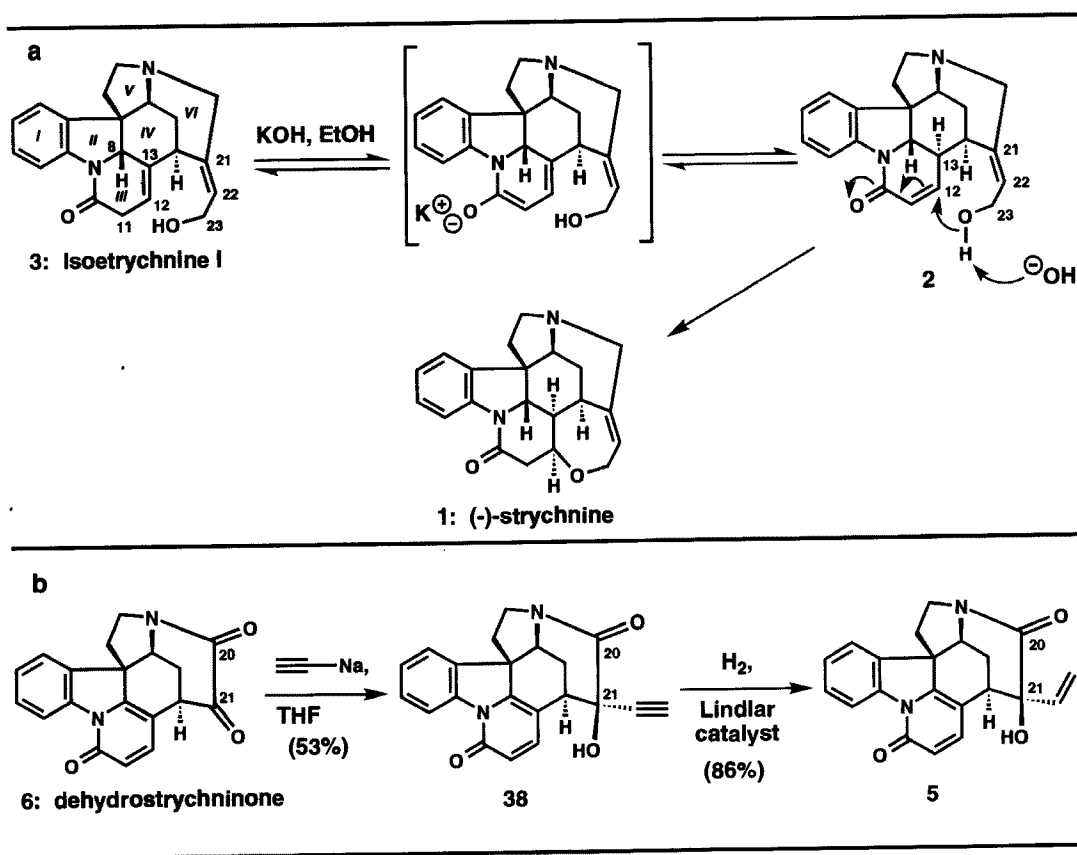
When **35** is exposed to aqueous hydrochloric and acetic acids under vigorous conditions, its enol acetate and *N*-acetyl moieties undergo hydrolysis to give amino ketone **8** (Scheme 7). Interestingly, oxidation of **8** with selenium dioxide in ethanol provides dehydrostrychninone (**6**), a substance found to be identical with a sample derived from natural sources. It was presumed that the action of selenium dioxide on **8** leads to the formation of *trans*-glyoxal **36**. With a 1,2-dicarbonyl grouping, *trans*-glyoxal **36** would be expected to undergo ready enolization towards C-14, an event that would permit an equilibrium to be established between *trans*-**36** and the corresponding *cis* epimer, intermediate **7**. Although such an equilibrium would likely be shifted in favor of



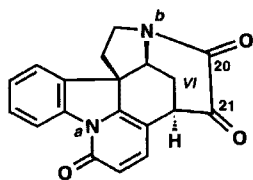
Scheme 7. Synthesis of intermediate **6**.

the less crowded *trans*-glyoxal stereoisomer (**36**), it is important to note that *cis*-glyoxal **7** can, once formed, participate in a productive cyclization reaction to give **37**. The close spatial relationship between N^b and the aldehydic C-20 carbonyl in **7**, and the tendency of 1,2-dicarbonyl systems to achieve the tetrahedral condition would drive the cyclization event. Finally, under the reaction conditions, oxidation of **37** occurs to give dehydrostrychnine (**6**).

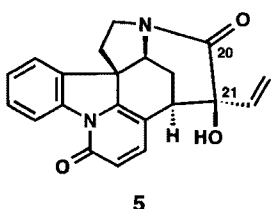
We have reached an advanced stage in Woodward's synthesis. We have retraced the elegant and straightforward sequences of reactions that have led to the synthesis of intermediate **6**, a molecule possessing six rings and functionality suitable for the elaboration of the seventh and final ring of strychnine. It is important to note that when Woodward's synthesis began, it was already known that the strychnine degradation product, isostrychnine I (**3**), could be reconverted to strychnine (**1**) upon treatment of the former substance with potassium hydroxide in ethanol (see Scheme 8a).¹⁰ Ethanolic



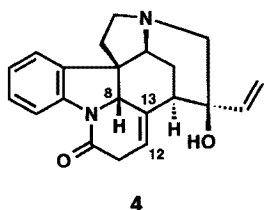
Scheme 8. Base-induced conversion of **3** to **1** (a) and synthesis of intermediate **5** (b).



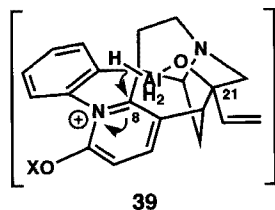
6: dehydrostrychninone



5



4

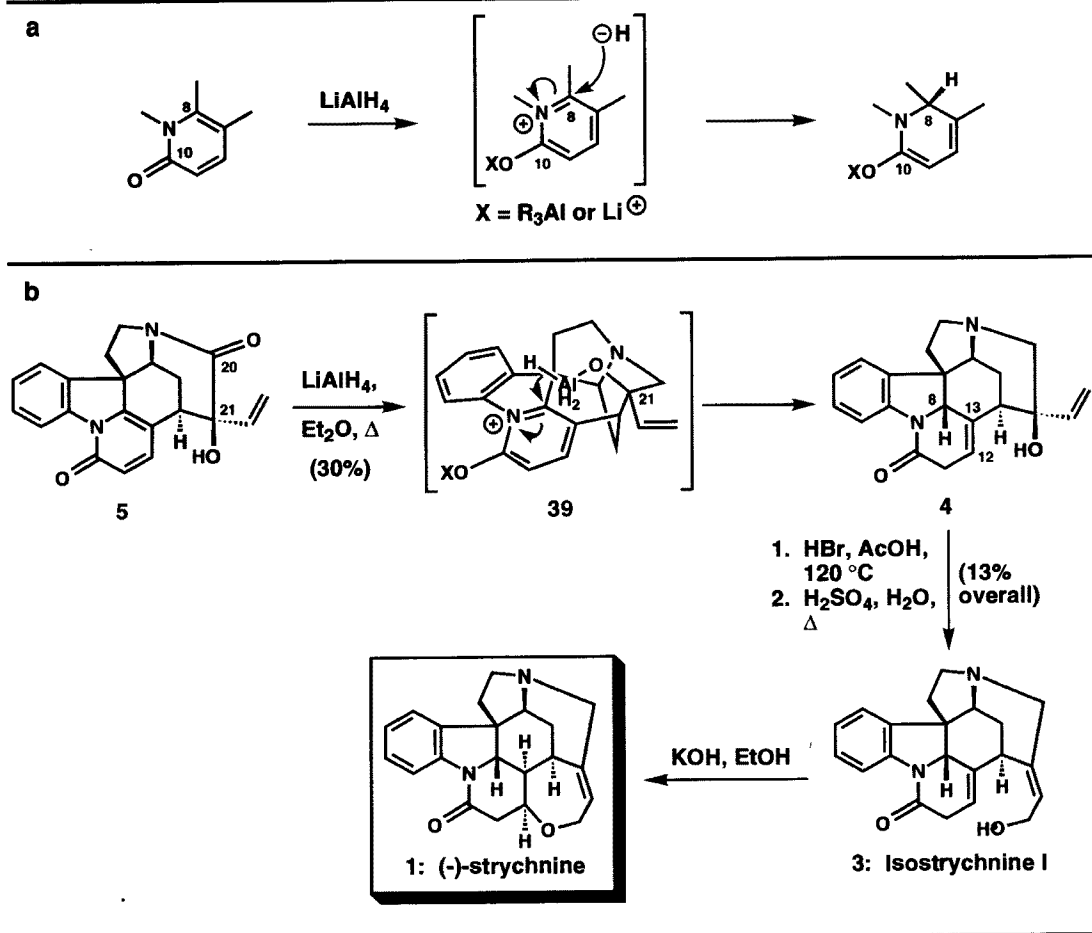


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potassium hydroxide initiates an equilibration of isostrychnine I (**3**) with its α,β -unsaturated isomer (**2**). With an electrophilic carbon atom at position 12 and with a nucleophilic alkoxide ion confined to a neighboring region of space by the $\Delta^{21,22}$ double bond, **2** is poised for an intramolecular Michael addition reaction to give strychnine (**1**). The overall process accomplishes the stereoselective creation of the vicinal stereocenters at C-12 and at C-13, and the formation of the seven-membered ether ring. The synthetic problem is thus reduced to the preparation of isostrychnine I (**3**) because the path to strychnine from this substance had already been laid down in 1948.¹⁰

In order to achieve the goal of synthesizing isostrychnine I (**3**) from dehydrostrychninone (**6**), the C-20 lactam carbonyl and the aromatic α -pyridone ring must both be reduced, and the C-21 ketone must be homologated (see Scheme 8b). With respect to the latter objective, it was found that treatment of a solution of **6** in THF with sodium acetylide results in the formation of propargylic alcohol **38** (53 % yield) (see Scheme 8b). As expected, the addition of acetylide ion to the reactive C-21 ketone carbonyl takes place selectively from the relatively unhindered convex face of the molecule to give the C-21 β -hydroxyl diastereoisomer. The conversion of **38** to allylic alcohol **5** is achieved smoothly (86 % yield) with hydrogen in the presence of Lindlar catalyst, and sets the stage for the crucial pyridone ring reduction step.

In a most impressive transformation, the C-20 amide carbonyl and the α -pyridone ring are both reduced in the desired manner by lithium aluminum hydride in refluxing ether to give **4** (see Scheme 9b). A consequence of the reduction of the α -pyridone ring to the desired $\Delta^{12,13}$ -dihydro- α -pyridone oxidation level is the creation of a stereogenic center at C-8. The observation that the newly introduced C-8 hydrogen atom occupies the much more hindered side of the molecule, and that the pyridone ring carbonyl is not reduced by lithium aluminum hydride are both striking aspects of this reduction process. With reference to Scheme 9a, it was reasoned that the mechanism of the pyridone reduction involves prior coordination of the C-10 amide carbonyl oxygen with a Lewis acid (i.e. R_3Al or Li^+) to afford a cationic intermediate which is susceptible to reduction through hydride delivery at C-8 (strychnine numbering). Ample precedent for this type of reduction process was available at the time, and it is important to recognize that the C-10 amide carbonyl, protected as it is in the form of an enolate, would be expected to survive the reduction. To account for the stereoselectivity exhibited in the reduction of **5**, it was proposed that the C-21 aluminum alkoxide, which forms when **5** is treated with lithium aluminum hydride, is positioned such that it can enforce an intramolecular delivery of hydride to C-8 (see intermediate **39**); the intramolecular delivery of hydride would thus proceed across the more hindered concave face of the molecule to give the observed and desired C-8 epimer.



Scheme 9. Pyridone ring reduction (a) and synthesis of (-)-strychnine (1) (b).

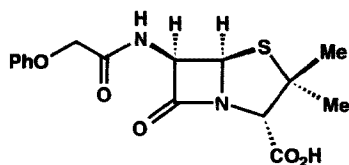
The structural homology between intermediate **4** and isostrychnine I (**3**) is obvious; intermediates **3** and **4** are simply allylic isomers and the synthetic problem is now reduced to isomerizing the latter substance into the former. Treatment of **4** with hydrogen bromide in acetic acid at 120°C results in the formation of a mixture of isomeric allylic bromides which is subsequently transformed into isostrychnine I (**3**) with boiling aqueous sulfuric acid. Following precedent established in 1948¹⁰ and through the processes outlined in Scheme 8a, isostrychnine I (**3**) is converted smoothly to strychnine (**1**) upon treatment with potassium hydroxide in ethanol. Woodward's landmark total synthesis of strychnine (**1**) is now complete.

2.4 Conclusion

The chemical synthesis of strychnine by Woodward *et al.* is a spectacular achievement of organic synthesis. It displays brilliant ingenuity and it ushered in the dawn of the golden era of organic synthesis. Furthermore, it gave chemists the confidence that nature's most complicated molecules *could* be made by total synthesis. The most striking feature of this landmark feat is its enforced reliance on only simple reagents to carry out nontrivial structural transformations. The oxidative cleavage of the veratryl ring in intermediate **17** is particularly interesting. This daring transformation can probably be traced to Woodward's novel proposal that the oxidative scission of an aromatic ring may constitute a key step in the biosynthesis of the *Strychnos* alkaloids.¹¹

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1: penicillin V

J. C. Sheehan (1957)

Penicillin V

3.1 Introduction

The fascinating history of the β -lactam antibiotics began in the late 1920s with Sir Alexander Fleming's historic discovery of a substance capable of destroying pathogenic bacteria. This substance is produced in nature by the mold *Penicillium notatum* and it was aptly named penicillin.¹ Approximately ten years after Fleming's discovery, Chain, Florey and coworkers reported that penicillin displays remarkable *in vivo* activity against a variety of pathogens.² In recognition of their pioneering contributions to the development of the wonder drug, penicillin, Fleming, Florey, and Chain shared the Nobel Prize for medicine and physiology on December 11, 1945.

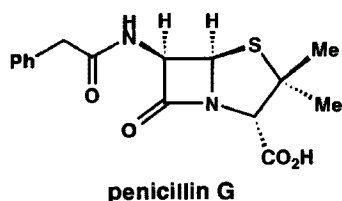
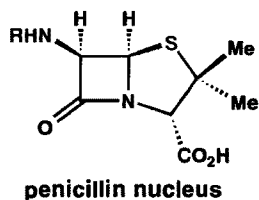
We are in no position to address the many significant events constituting penicillin's colorful past. This monumental task was accepted by Professor J. Sheehan, an eminent organic chemist and a major figure in the penicillin field.³ Nevertheless, it is interesting to note that the promising chemotherapeutic potential of penicillin motivated the institution of a massive, cooperative British-American program during the Second World War which had as its principal objectives the elucidation of the molecular structure of penicillin, the development of a practical path for its production by chemical synthesis, and the large-scale production of penicillin by fermentation methods. Approximately one thousand chemists representing both academic and industrial institutions participated in this unprecedented British-American scientific venture.⁴ Despite concentrated efforts by some of the greatest organic chemists ever known and substantial investments by both countries, the goal of achieving a practical synthesis of penicillin before the end of the

war could not be reached.⁵ By contrast, the procurement of sufficient quantities of penicillin by fermentation was found to be feasible and this led to the practical use of penicillin to combat infection before the end of the war. Many, many lives were saved as a result and penicillin would forever occupy a very important place in medicine.

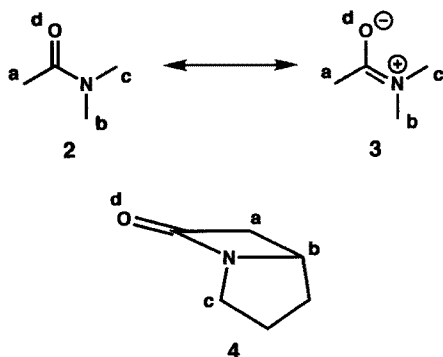
Even at the end of World War II, there was considerable uncertainty in the scientific community regarding the structure of penicillin. The controversy surrounding the constitution of this molecule raged on until Professor Dorothy Crowfoot-Hodgkin of Oxford University elucidated the structure of penicillin G by X-ray crystallography.⁶ When addressing penicillin, it is sometimes more appropriate to use the plural term "penicillins" because nature provides a family of closely related substances which differ only with respect to the acyl grouping attached to the nitrogen atom that is α to the lactam carbonyl. Thus, unless we refer to a particular member of the penicillin family, the word "penicillin" actually includes each member.

Before Professor Crowfoot-Hodgkin's major contribution in 1945, few chemists had faith in the proposal that penicillin's structure is distinguished by a β -lactam ring even though considerable evidence had been accumulated during the Anglo-American penicillin project that was consistent with the β -lactam structure. Of course it is now well known that the β -lactam moiety is responsible for penicillin's chemical lability and biological activity. Destruction of penicillin's β -lactam ring, a feat that can be easily achieved, deprives penicillin of its potent antibacterial properties. By virtue of penicillin's marked lability, and given the limitations of organic synthesis methodology in the 1940s, it is certainly not surprising that successes in its synthesis were few and far between. The development of a practical laboratory synthesis of the penicillin molecule was eventually regarded as the "impossible problem".³

The most striking and challenging structural feature of penicillin is its four-membered β -lactam ring; this strained substructure is the locus of penicillin's unstable and reactive nature and is responsible for its potent antibacterial properties. However, the strain inherent in a four-membered β -lactam ring is not enough to account for the fragility of penicillin's ring because simpler, monocyclic β -lactams are, in many cases, rather stable substances. For example, whereas simple β -lactams are not readily susceptible to hydrolysis, the β -lactam ring of the penicillins is easily cleaved in either acidic or basic media. Indeed, many attempts to form the β -lactam ring of the penicillins through lactamization protocols using acid halide and acid anhydride forming reagents (e.g. phosphorous trichloride, thionyl chloride, acetyl chloride, and acetic anhydride) failed miserably because of the instability of the penicillin β -lactam ring under acidic conditions.⁷ To achieve the formation of the penicillin β -lactam ring through lactamization would require the development of new, mild methods.



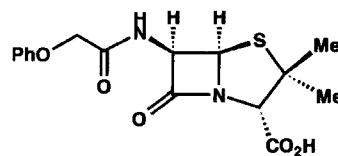
It was R. B. Woodward who, in the early 1940s, accounted for the marked lability of the β -lactam ring of the penicillins.⁸ In the case of a typical amide, the lone electron pair on nitrogen can delocalize into the adjacent carbonyl (see **2** \leftrightarrow **3**, Scheme 1). This favorable interaction confers a great deal of stability to amides and attenuates the electrophilic character of the amide carbonyl group. An amide is the beneficiary of substantial stabilization energy only if the attached groups a, b, c, and d can reside in a common plane. Woodward reasoned that the β -lactam ring of the penicillins does not exhibit the stability of a typical amide because it is fused to a five-membered ring (see intermediate **4**) and, as a result, it cannot accommodate the requisite parallel alignment of the carbonyl π system and nitrogen's unshared electron pair. The inherent acylating potential of the β -lactam ring of the penicillins approximates that of a carboxylic acid chloride.^{8a}



Scheme 1. Amide resonance.

Over the course of approximately ten years and in the face of great difficulties, Professor J. Sheehan and his group at MIT persevered, and their efforts culminated in the first rational total synthesis of penicillin V (**1**) in 1957.^{9,10} This impressive feat stands as a great achievement in organic synthesis. The daunting challenge that penicillin presented to organic synthesis is evident in the following analogy made by J. Sheehan: "At the time of my successful synthesis of penicillin V in 1957, I compared the problem of trying to synthesize penicillin by classical methods to that of attempting to repair the mainspring of a fine watch with a blacksmith's anvil, hammer, and tongs".¹¹

Sheehan's concentrated attack upon the penicillin synthesis problem began in 1948 and was conducted on a broad front. It was anticipated at the outset that the formidable penicillin V molecule would succumb to organic synthesis only in the event that new powerful and selective methods of organic synthesis are brought to bear on the problem. But, in addition, and perhaps more importantly, these new synthetic methods must be mild enough to contend with

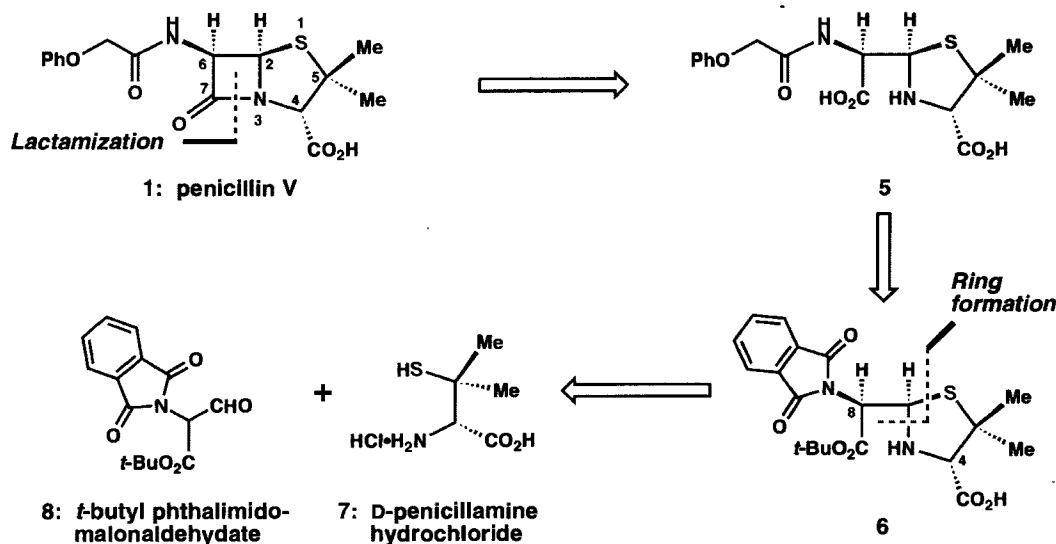


1: penicillin V

the “diabolic concatenations of reactive groupings”¹² that are characteristic of the penicillins. The remainder of this chapter is devoted to Sheehan’s classic synthesis of penicillin V (**1**) as its potassium salt. Its general features are outlined retrosynthetically in Scheme 2.

3.2 Retrosynthetic Analysis and Strategy

The sensitivity of the β -lactam ring of **1** mandates that its construction be deferred to a late, preferably the last, stage of the synthesis. Thus, retrosynthetic cleavage of the β -lactam ring, in the manner illustrated in Scheme 2, furnishes penicilloic acid **5** as a potential precursor. This retrosynthetic maneuver introduces the interesting possibility of creating the strained four-membered ring of penicillin V by a direct cyclization or lactamization reaction. Interestingly, during the early stages of Sheehan’s fruitful penicillin project, a number of novel strategies for β -lactam formation were developed which did not involve lactamization.¹³ Sheehan’s early work was most likely guided by the assumption that lactamization protocols would not serve well in the context of a penicillin synthesis. After all, the consistent failures of traditional lactamization strategies were well documented during the wartime penicillin project. Suffice it to say, a new and mild lactamization method would have to be developed before the attractive and direct conversion of **5** to **1** could be achieved; the lactamization protocols available at the outset of Sheehan’s penicillin studies were simply too harsh for this objective.



Scheme 2. Retrosynthetic analysis of penicillin V (**1**).

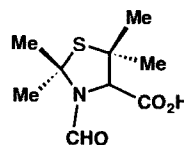
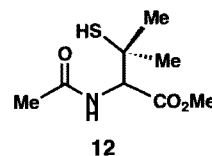
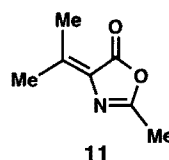
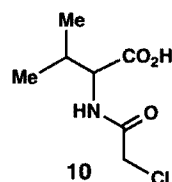
Penicilloic acid **5**, the substrate for the projected lactamization reaction, could be derived from the suitably protected intermediate **6**. Retrosynthetic disassembly of **6**, in the manner illustrated, provides D-penicillamine hydrochloride (**7**) and *tert*-butyl phthalimidomalonaldehyde (**8**) as potential building blocks. In the synthetic direction, it is conceivable that the thiol and amino groupings in **7** could be induced to converge upon the electrophilic aldehyde carbonyl in **8** to give thiazolidine **6** after loss of a molecule of water. The details of Sheehan's convergent penicillin synthesis strategy are presented in Schemes 3–5.

3.3 Total Synthesis

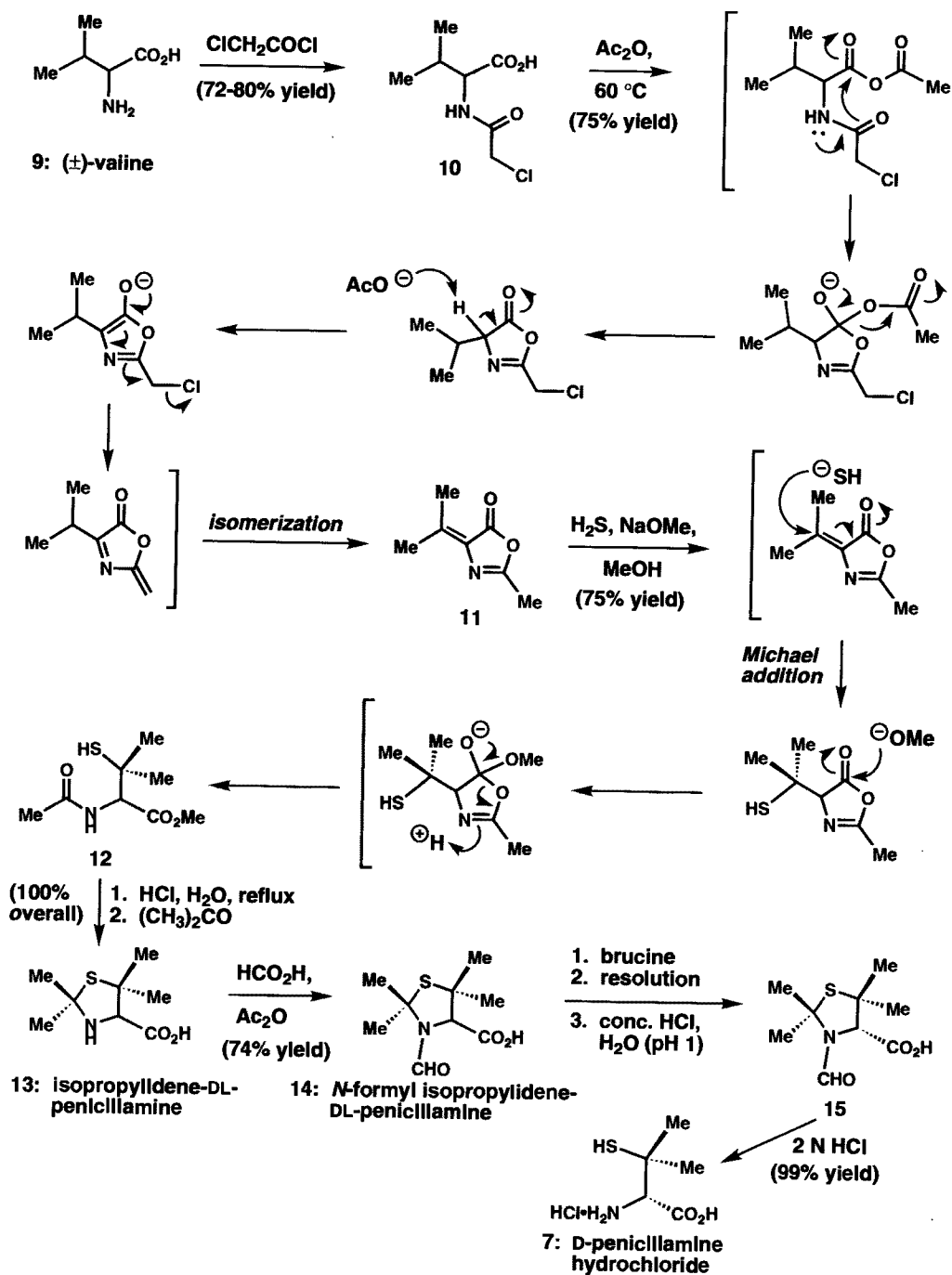
The reactions employed to achieve the synthesis of intermediates **7** and **8** are presented in Schemes 3 and 4, respectively. It was known at the time that both enantiomers of penicillamine hydrochloride (**7**) could be obtained in pure form by the route illustrated in Scheme 3. The starting material for this interesting sequence is racemic valine (**9**), and the first step is a straightforward *N*-acylation using chloroacetyl chloride to give **10**. The action of acetic anhydride on **10** could conceivably generate, as a transient intermediate, a mixed anhydride that subsequently undergoes conversion to oxazolone **11** through the processes illustrated in Scheme 3.

By virtue of its constitution, **11** is a competent Michael acceptor and it undergoes ready conversion to intermediate **12** upon treatment with hydrogen sulfide and sodium methoxide. The thiol reacts in a chemoselective fashion with the electrophilic β carbon of **11** (see arrows) and the heterocyclic ring suffers cleavage by methoxide ion to give the observed product. After hydrolytic cleavage of both *N*-acetyl and methoxycarbonyl groupings with aqueous HCl, the contiguous thiol and amino functions can be simultaneously protected in the form of a thiazolidine ring with acetone. Treatment of isopropylidene-DL-penicillamine (**13**) with formic acid and acetic anhydride results in the formation of *N*-formyl isopropylidene-DL-penicillamine (**14**), a substance that can be readily resolved with brucine. Indeed, reaction of brucine with racemic **14** in water furnishes a diastereomeric mixture of salts. The brucine salt of *N*-formyl isopropylidene-D-penicillamine selectively crystallizes from the reaction mixture and can be collected by filtration. Treatment of an aqueous solution of this brucine salt with concentrated HCl provides *N*-formyl isopropylidene-D-penicillamine (**15**). Further treatment of this substance with hot 2 *N* HCl liberates enantiomerically pure D-penicillamine hydrochloride (**7**). The identity of **7** was established by comparison of its physical properties with those of D-penicillamine hydrochloride derived from natural penicillin.

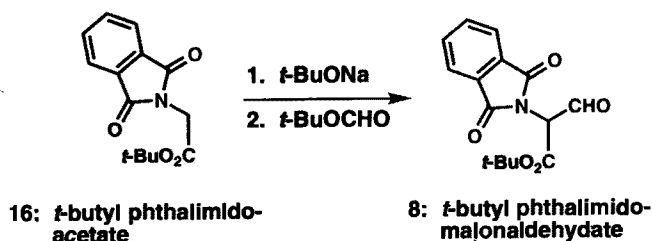
tert-Butyl phthalimidomalonaldehyde (**8**) can be prepared in one step from *tert*-butyl phthalimidoacetate (**16**) (see Scheme 4).¹⁵



14: *N*-formyl isopropylidene-DL-penicillamine



Scheme 3. Synthesis of intermediate 7.

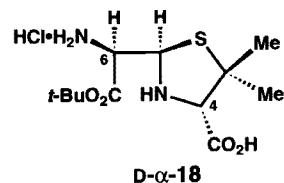
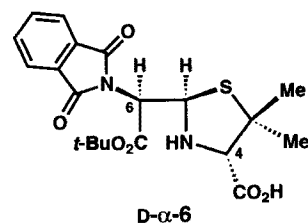


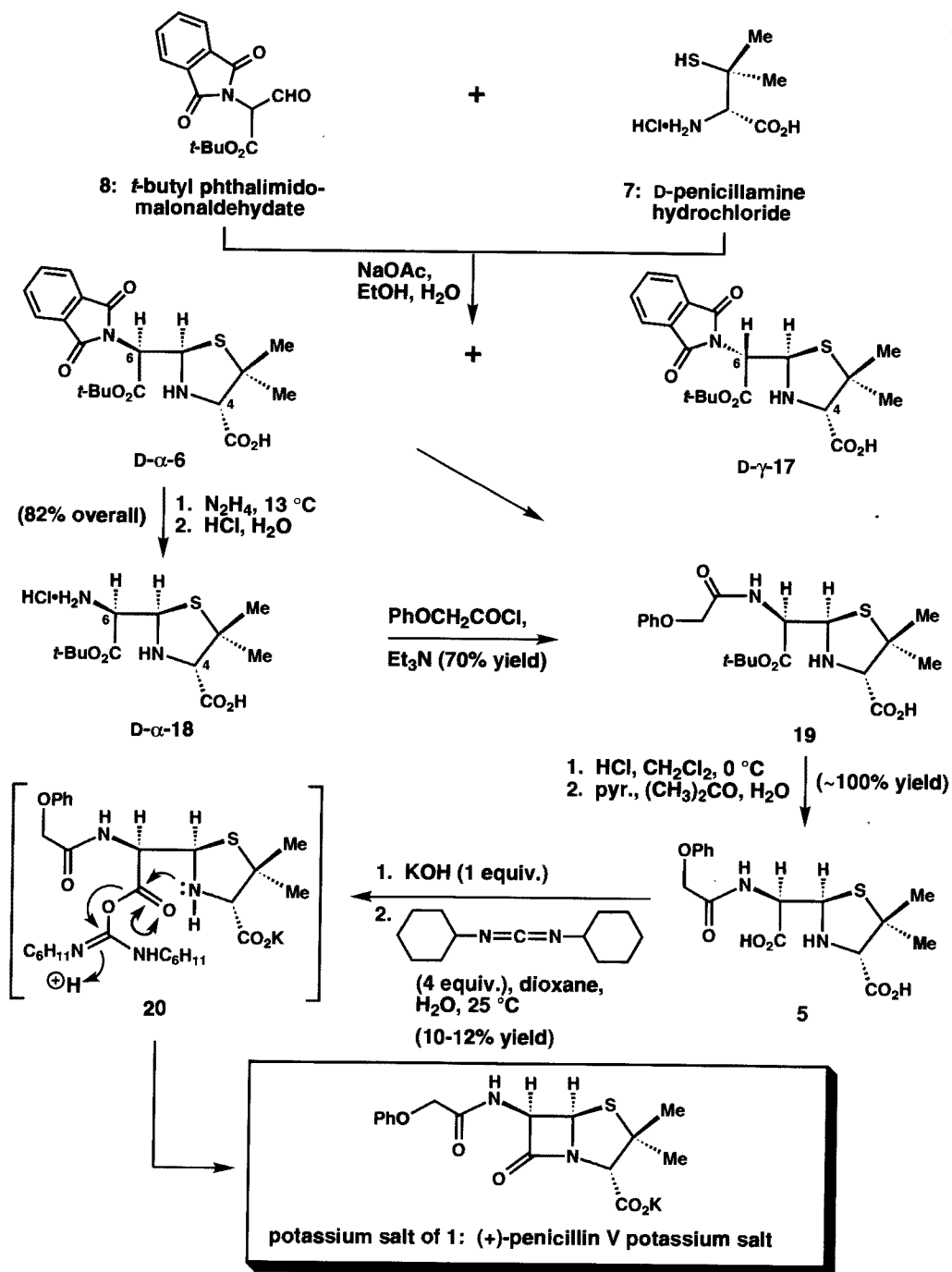
Scheme 4. Synthesis of intermediate **8**.

Exposure of compound **16**, a substance that can be obtained in a straightforward manner from glycine, to sodium *tert*-butoxide furnishes an enolate that undergoes conversion to **8** upon treatment with *tert*-butyl formate. It was anticipated that the phthalimido and *tert*-butyl ester protecting groups in **8** could be removed easily and selectively under anhydrous conditions at a later stage in the synthesis.

The convergent union of intermediates **7** and **8** can be brought about smoothly by combining these two substances in aqueous ethanol buffered with sodium acetate (see Scheme 5). In this simple reaction, the adjacent amino and thiol functions of **7** converge upon the electrophilic aldehyde carbonyl of intermediate **8**; a molecule of water is expelled and a mixture (*ca.* 1:1) of diastereomeric thiazolidines, epimeric at C-6, is produced. In this reaction, racemic aldehyde **8** is joined with enantiomerically pure **7** to give a molecule that contains three stereocenters. Although the configuration of the carboxyl-bearing stereocenter in **7** is conserved during the course of this reaction, the convergent union of intermediates **7** and **8** could, in theory, result in the formation of four distinct thiazolidine stereoisomers. In the event, however, only two diastereomers, epimeric at C-6, are produced. The desired thiazolidine stereoisomer, intermediate **6**, is referred to as the *D*- α isomer; it corresponds, in absolute configuration, to natural penicillin. Interestingly, heating a pyridine solution of the undesired *D*- γ isomer **17** establishes an equilibrium between the *D*- γ isomer and the *D*- α isomer; the desired *D*- α -**6** crystallizes upon cooling, and the filtrate containing *D*- γ -**17** can be recycled. In this reaction, pyridine induces epimerization at C-6 in **17** and the desired *D*- α isomer is produced to the extent of 25 %. This equilibration/recycling process permits the productive utilization of the undesired *D*- γ isomer and therefore enhances overall synthetic efficiency.

Intermediate *D*- α -**6** must now be converted into a form amenable to the crucial lactamization reaction. To this end, treatment of *D*- α -**6** with hydrazine accomplishes the removal of the phthalimide protecting group and provides *D*- α -**18** (Scheme 5) after acidification with dilute aqueous HCl. It is noteworthy that the acid-labile *tert*-butyl ester function withstands the latter step. Introduction of the





Scheme 5. Synthesis of the potassium salt of (+)-penicillin V (1).

phenoxyacetyl side chain, a characteristic feature of penicillin V, is achieved easily at this stage by treatment of D-**a-18** with phenoxyacetyl chloride and triethylamine (see D-**a-18** → **19**).

It is instructive to preface the next reaction with a few remarks about *tert*-butyl esters. In synthesis, it is common practice to achieve the conversion of an ester to the corresponding carboxylic acid through basic hydrolysis (e.g. LiOH, THF-H₂O). The basic hydrolysis of an ester is a process that is known as *saponification* and it generally works very well. Although the action of hydroxide ion on a *tert*-butyl ester could conceivably accomplish its hydrolysis, the *tert*-butoxycarbonyl function undergoes facile conversion to a carboxyl group in the presence of anhydrous Brønsted acids. The susceptibility of *tert*-butyl esters to cleavage with anhydrous Brønsted acids was first exploited by Sheehan *et al.* during the early stages of their penicillin synthesis program.¹⁶ In the case at hand, *a-tert*-butyl D-phenoxyethylpenicilloate (**19**) undergoes near-quantitative conversion to the key lactamization substrate **5** upon treatment with anhydrous HCl, followed by recrystallization of the resultant carboxylic acid ammonium salt from aqueous acetone containing one equivalent of pyridine. As expected, the *tert*-butyl ester grouping in **19** suffers ready cleavage in the presence of anhydrous HCl. Incidentally, the hydrogenolysis of a benzyl ester to the corresponding carboxylic acid¹⁷ is a very efficient transformation that serves well when neither basic nor acidic reaction conditions are tolerated.

It is appropriate, at this juncture, to acknowledge an important advance in the state of the art for forming amide bonds. In 1955, Sheehan's group reported that amide linkages form smoothly upon treatment of a mixture of a carboxylic acid and an amine in water at room temperature with *N,N'*-dicyclohexylcarbodiimide (DCC).¹⁸ The use of an aliphatic carbodiimide for the construction of an amide bond was unprecedented when Sheehan *et al.* disclosed, in 1955, the facility with which the amino group of one amino acid derivative can be coupled with the free carboxyl group of another using DCC as a dehydrating agent. The overall process involving initial *in situ* activation of a carboxyl group with DCC followed by subsequent reaction with an amine to give an amide can be conducted under very mild conditions (i.e. room temperature, neutral pH) and, usually, in excellent yield.¹⁹ For these reasons, it was anticipated that DCC might permit the construction of the reactive β -lactam ring of the penicillin V molecule. In the event, addition of four equivalents of DCC to a dilute solution of the monopotassium salt of **5** in dioxane-water at 25 °C results in the formation of penicillin V potassium salt in 10–12 % yield. Although the mechanism for this step could conceivably involve the intramolecular attack of the thiazolidine nitrogen atom upon a symmetrical anhydride, the proximity of the reacting groups and more recent mechanistic studies²⁰ favor the intramolecular addition of the thiazolidine nitrogen to the activated carbonyl of an *O*-acylisourea (see intermediate **20**, Scheme 5). In spite of the low yield for the crucial lactamization

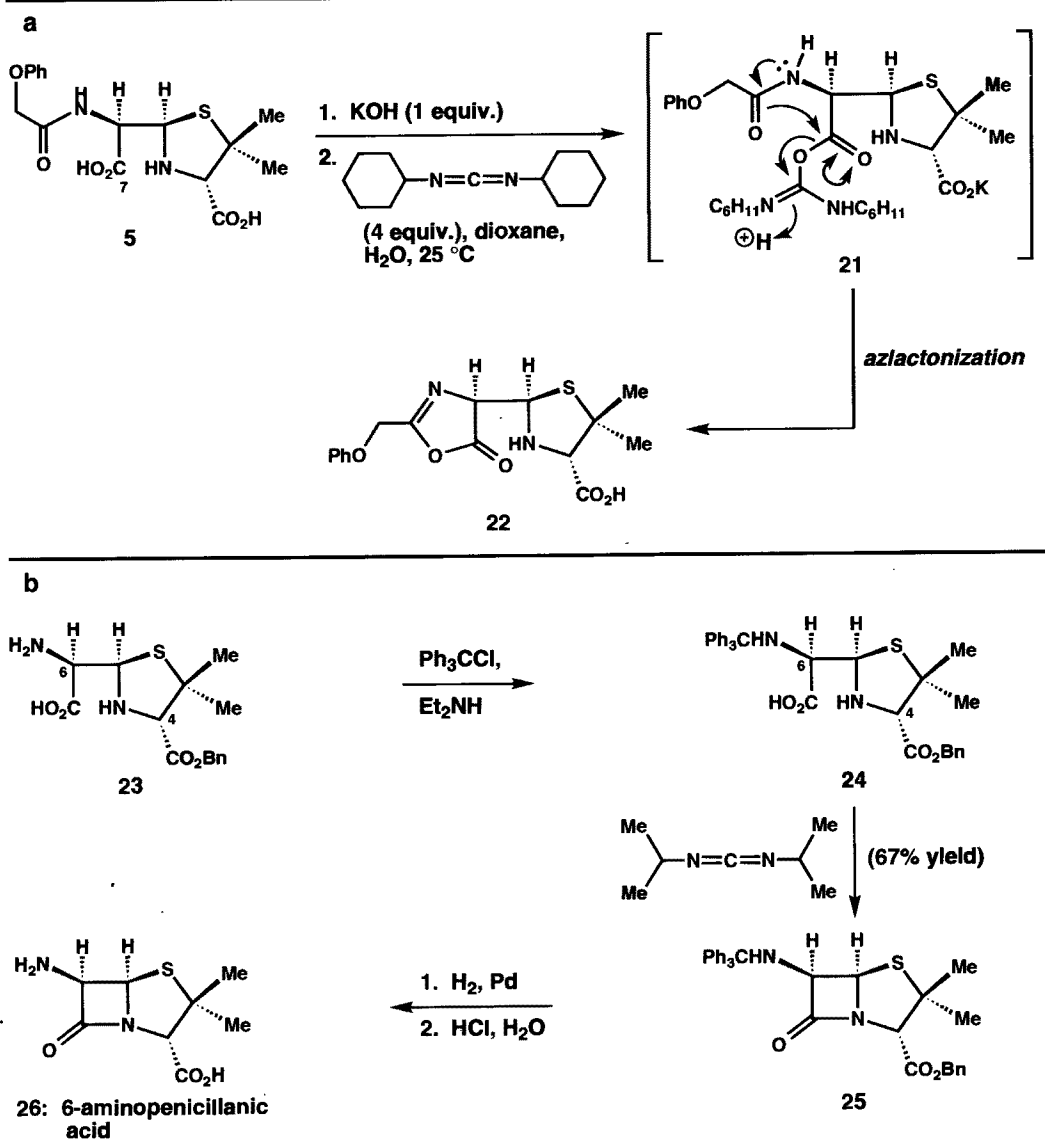
step, the first rational synthesis of a natural penicillin has been achieved. Indeed, the synthetic crystalline potassium salt of penicillin V (**1**) was found to be identical to the potassium salt of natural penicillin V with respect to physical properties and biological assay comparisons.

It would be instructive to inquire about the factors that undermine the success of the lactamization step. If we examine the structure of intermediate **5**, we find that this substance contains the phenoxyacetyl side chain that distinguishes penicillin V from the other natural penicillins. The amide function of this side chain, the amide oxygen atom in particular, possesses nucleophilic properties. Upon activation of the free carboxyl function at position 7 in **5** with DCC, the Lewis-basic amide oxygen atom can, by virtue of its proximity to the activated carbonyl, compete as a nucleophile with the thiazolidine ring nitrogen (see **5** → **21** → **22**, Scheme 6a). The intramolecular interception of an activated C-7 carbonyl by the side chain amide oxygen atom is a process that is known as *azlactonization*. Azlactone formation is one reason why the numerous wartime attempts to close the penicillin β -lactam ring through lactamization failed.²¹ Azlactone formation at any stage of a penicillin synthesis would constitute a serious setback because the conversion of an oxazolone such as **22** to the isomeric β -lactam structure with base is not feasible. It seems reasonable to expect that the yield for the crucial lactamization reaction might increase substantially if the propensity for azlactone formation can be attenuated or, better still, eliminated all together.

In subsequent studies,²² Sheehan *et al.* demonstrated that the action of diisopropylcarbodiimide on penicilloate **24**, prepared by protection of the free primary amino group in **23** with trityl chloride (see Scheme 6b), results in the formation of the desired β -lactam **25** in a very respectable yield of 67%. In this most successful transformation, the competing azlactonization reaction is prevented by the use of a trityl group (Ph₃C) to protect the C-6 amino function. Hydrogenolysis of the benzyl ester function in **25**, followed by removal of the trityl protecting group with dilute aqueous HCl, furnishes 6-aminopenicillanic acid (**26**), a versatile intermediate for the synthesis of natural and unnatural penicillins.

3.4 Conclusion

During the course of the British-American wartime penicillin project, a large body of information relevant to the constitution and chemistry of the penicillins was uncovered. It was recognized at an early stage that the penicillins are assembled from a relatively small number of atoms, and this observation spurred hopes that a practical path for a chemical synthesis of the penicillins could be found before the end of the war. Although the atoms that constitute the



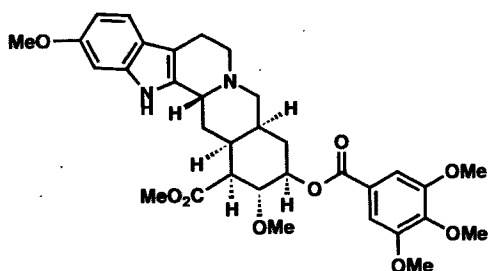
Scheme 6. Azlactonization of intermediate **5** (a) and synthesis of 6-aminopenicillanic acid (b).

penicillin V molecule account for a molecular mass of only 350, a pathway for total synthesis was by no means easy to find. Roughly twelve years intervened between the end of World War II and the disclosure of the first chemical synthesis of a natural penicillin by Sheehan and Henery-Logan. To solve what was once regarded as the "impossible problem," Sheehan *et al.* developed and utilized several synthetic methods of general utility. The employment of readily cleavable phthalimide and *tert*-butyl ester protecting groups, and the use of an aliphatic carbodiimide to close the recalcitrant penicillin β -lactam ring are noteworthy features of this synthesis. The total synthesis of penicillin V by Sheehan and his group must be regarded as a milestone in organic synthesis.

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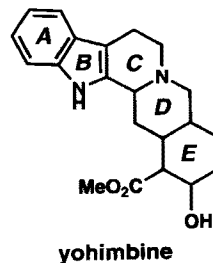
1: reserpine

R. B. Woodward (1958)

Reserpine

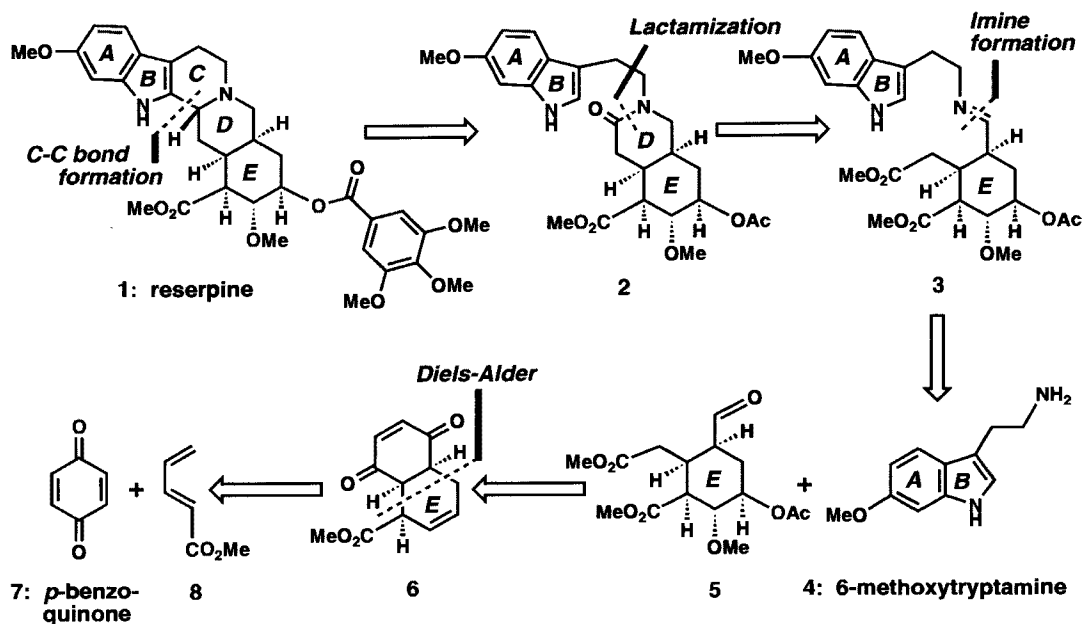
4.1 Introduction

Contained within the extracts of the Indian snakeroot *Rauwolfia serpentina* Benth. is an alkaloid that exerts a profound effect on the central nervous system. It was first isolated in 1952 by Schlittler *et al.* and given the name reserpine.¹ When exposed to reserpine, postganglionic adrenergic neurons containing norepinephrine are altered in an irreversible manner resulting in a depletion of the neurotransmitter substance.² This unique mode of action is responsible for reserpine's effectiveness in the treatment of hypertensive, nervous, and mental disorders. A year after their initial report, Schlittler and his colleagues disclosed the basic structure of reserpine and demonstrated its relationship to a large class of alkaloids of which yohimbine (of which there are several stereoisomers) is the prototype.³ Thus, in 1953, the constitution of reserpine was known. However, the problem of defining the stereochemical details inherent in reserpine's structure remained elusive until the Ciba group and a number of other investigators independently reported, in 1955, their studies which permitted the structure of reserpine (**1**) to be fully characterized.⁴ In 1955, the stage was therefore set for serious synthetic studies. In the subsequent year, the first total synthesis of reserpine was disclosed by the late Professor R. B. Woodward and his colleagues at Harvard.⁵ Considered by some to be one of Woodward's greatest contributions to organic synthesis, the total synthesis of reserpine (**1**) by the Woodward group is particularly striking in the way that it manipulates molecular conformations to achieve important synthetic objectives.



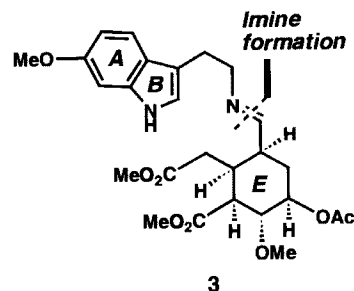
4.2 Retrosynthetic Analysis and Strategy

The general features of the synthesis of reserpine by Woodward are illustrated, in retrosynthetic format, in Scheme 1. Examination of reserpine's structure reveals that five out of a total of six stereogenic centers are contiguous and are concentrated in the E-ring of the alkaloid. Arranged around the six-membered ring of intermediate **5**, a fully functionalized representative of reserpine's E-ring, are five substituents properly oriented in space and suitably differentiated with respect to function. By skillfully manipulating the conformations of *cis*-decalin derivatives of **6**, it was projected that a short sequence of substrate-stereocontrolled transformations could accomplish the synthesis of key intermediate **5**. As a means of assembling highly functionalized cyclohexane derivatives, the Diels-Alder reaction is unmatched in terms of productivity; up to four contiguous asymmetric centers can be created in a single, stereospecific and usually regio- and diastereoselective (i.e. *endo* vs *exo*), operation.⁶ The Diels-Alder reaction is stereospecific because relative stereochemical relationships present in the diene and the dienophile are preserved throughout the course of the reaction. It was projected that intermediate **6** could be formed in a single operation through a Diels-Alder reaction between *para*-benzoquinone (**7**) and methyl vinylacrylate (**8**). The combination of dienophile **7** and diene **8** was expected to furnish, through a pre-



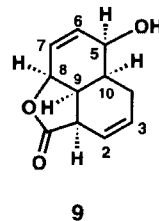
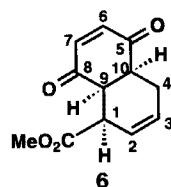
Scheme 1. Retrosynthetic analysis of reserpine (1).

ferred *endo* transition state geometry, intermediate **6**. The six-membered ring in intermediate **6** that will eventually be expressed in ring E of reserpine is already decorated with three stereogenic centers, and it possesses an appropriately placed π bond which can support the introduction of the remaining two stereogenic centers. The assembly of intermediate **5** would mark the achievement of the first synthetic objective. Contained within intermediate **5** is an aldehyde, and it was anticipated that in the presence of 6-methoxytryptamine (**4**), Schiff base intermediate **3** would form. A chemoselective reduction of the imine in **3** with sodium borohydride, followed by intramolecular cyclization, could then afford lactam **2**. As we shall see later in the synthesis, during the course of the conversion of intermediate **2** to reserpine (**1**), a clever tactic was employed which enforced the adoption of an unfavorable conformation and set the stage for a thermodynamically favored isomerization reaction; it provided an elegant solution to a serious stereochemical problem, and it is the most spectacular maneuver in the synthesis (*vide infra*).

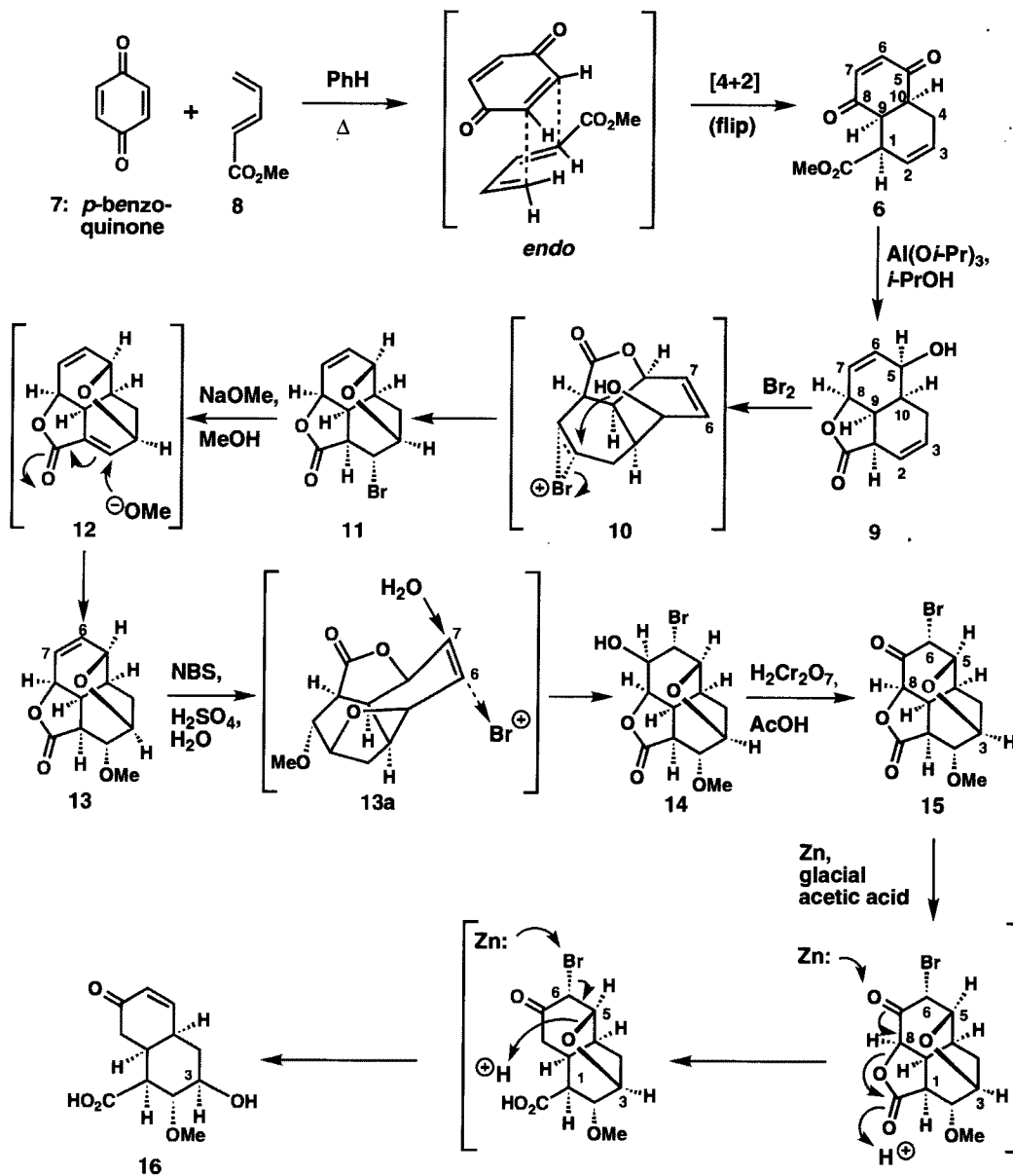


4.3 Total Synthesis

During the early stages in the synthesis of key intermediate **5**, important observations were made which formed the basis for an exceedingly efficient approach to the synthesis of this compound. Our journey begins with a Diels-Alder reaction between *para*-benzoquinone (**7**) and methyl vinylacrylate (**8**) (Scheme 2). This reaction proceeds smoothly in a solution of refluxing benzene and it gives, through a preferred *endo* transition state geometry, intermediate **6**. As we have already stated, the Diels-Alder reaction is stereospecific, and this most useful property ensures that the two rings in **6** are *cis*-locked. As a general rule, the *endo* adduct of a Diels-Alder reaction can be easily recognized as the one in which there is a *cis* relationship between the electron-withdrawing group in the dienophile and the substituent that is *trans* in the diene. By contrast, the *exo* adduct possesses a *trans* relationship between the dienophile electron-withdrawing group and the *trans* diene substituent. Thus, in this example, *para*-benzoquinone (**7**) possesses two electron-withdrawing groups in a *cis* relationship and, in *endo* adduct **6**, both are *cis* to the methyl ester that used to be *trans* in diene **8**. It is noteworthy that intermediate **6**, prepared in one step from simple starting materials, already possesses three out of the required five contiguous stereocenters. Meerwein-Ponndorf-Verley reduction⁷ of **6** accomplishes the reduction of both ketone carbonyl groups and gives, after lactonization, intermediate **9**.



A stereochemical issue of great importance presents itself here. In the chemoselective reduction of the two ketone carbonyls at C-5 and C-8 in **6**, the addition of hydride takes place on the same side



Scheme 2. Synthesis of intermediate 16.

of the molecule on which the two bridgehead hydrogens at C-9 and C-10 are located. It was known from the work of Barton *et al.*⁸ that hydride reductions of relatively unhindered carbonyl groups, afford, as the major product, equatorial alcohols. Thus, on the basis of this precedent, the selective formation of **9** is not so surprising. But, in addition and to the extent that steric factors influence the course of the reduction, intermediate **6**, like all *cis*-decalin derivatives, possesses a folded carbon framework to which access is very hindered on the concave face (see Figure 1). In this case, a stereoelectronic preference and the biased carbon framework of **6** mutually reinforce the indicated stereochemical course for the Meerwein-Ponndorff-Verley reduction.

During the course of a related model study, it was found that the $\Delta^{6,7}$ double bond is markedly resistant to attack by bromine at room temperature. This information was useful in devising the next tactic. Exposure of **9** to bromine in an inert solvent or even in methanol at room temperature induces a smooth intramolecular etherification reaction and gives intermediate **11**. In this stereospecific reaction, bromine engages the $\Delta^{2,3}$ double bond in **9** from its less hindered convex face, and elicits an intramolecular attack by the proximal C-5 hydroxyl group (see intermediate **10**). In the presence of sodium methoxide, a dehydrobromination reaction occurs to give the presumed intermediate **12**. The intermediacy of **12** is brief; it readily participates in a Michael addition reaction with methoxide to give intermediate **13**. In intermediate **13**, we now have a compound which possesses all five contiguous stereogenic centers found in the corresponding part of reserpine's E-ring and which is available in only three straightforward steps from intermediate **6**! Whereas the remaining carbon-carbon double bond in **13** resists attack by bromine at room temperature, it undergoes ready conversion to bromohydrin **14** in the presence of aqueous *N*-bromosuccinimide and sulfuric acid at 80°C. In the preferred conformation of **13**, the ring bearing the carbon-carbon double bond assumes a quasi-chair form and the other ring a slightly distorted boat form (see **13a**). Convex face attack of electrophilic bromine upon the $\Delta^{6,7}$ double bond, followed by interception of the bromonium ion by a molecule of water, leads to the formation of the diaxial *trans*-bromohydrin **14**. Oxidation of the secondary alcohol in **14** with chromic acid in acetic acid furnishes ketone **15**. When ketone **15** is treated with zinc metal in glacial acetic acid, two important events take place. The C-8-oxygen bond is reductively cleaved to give a free carboxyl group at C-1. In addition, the carbon-bromine bond in the other α position (C-6) and the 3,5-ether bridge are cleaved concomitantly to give intermediate **16**. It is interesting to note that the ether oxygen at C-5, which used to belong to *para*-benzoquinone (**7**), has been smoothly transferred to C-3 where it will eventually be expressed in ring E of reserpine.

The completion of the synthesis of key intermediate **5** now only requires a few modifications of **16** (see Scheme 3). Esterification of

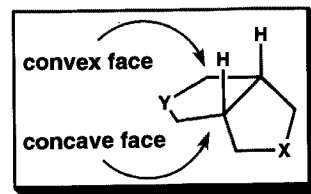
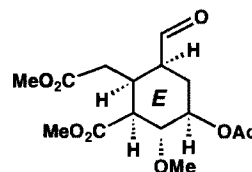
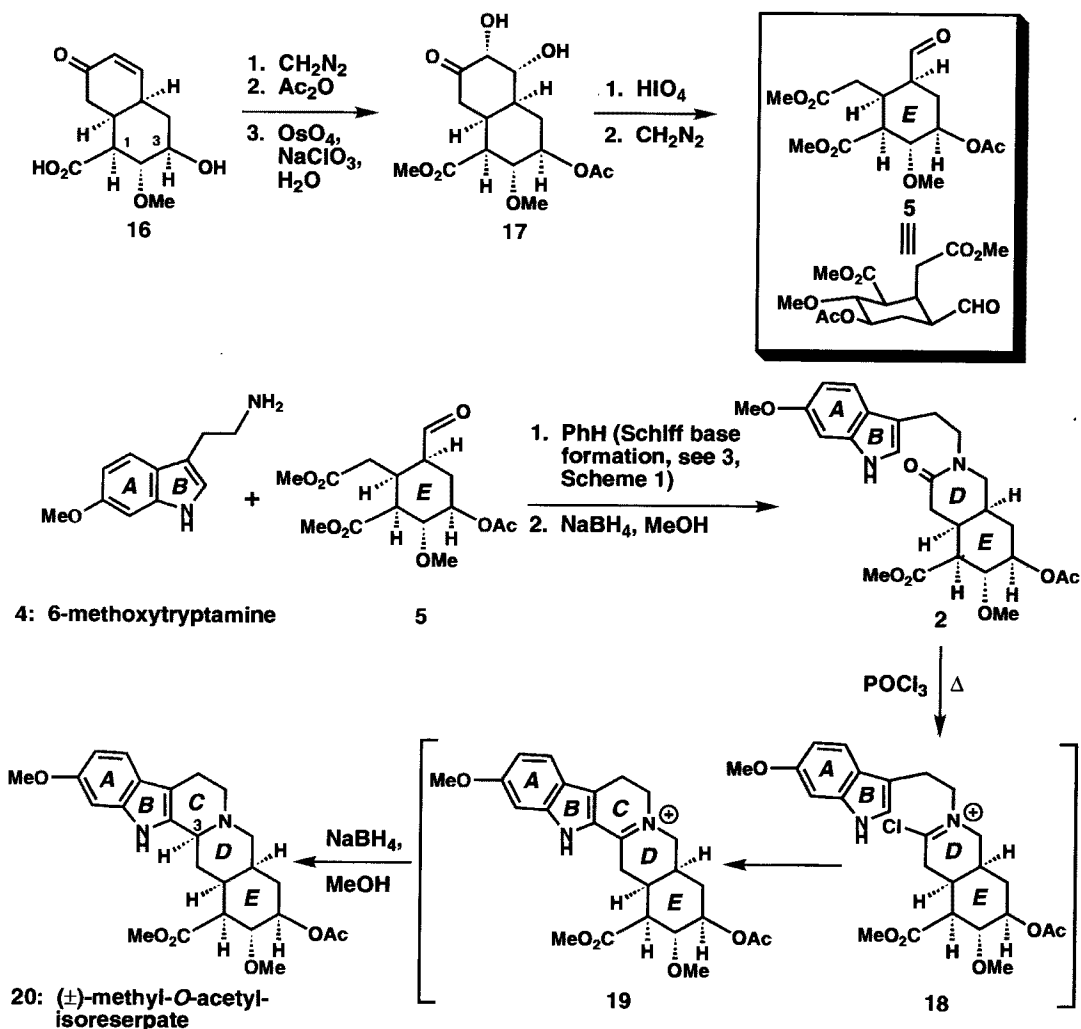


Figure 1. Convex and concave faces of a generic bicyclic system.





Scheme 3. Synthesis of (±)-methyl-O-acetyl-isoreserpate (**20**).

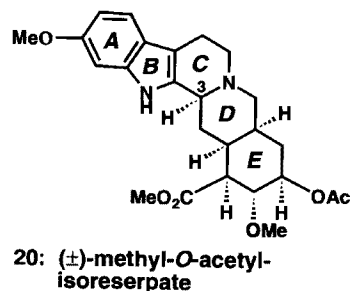
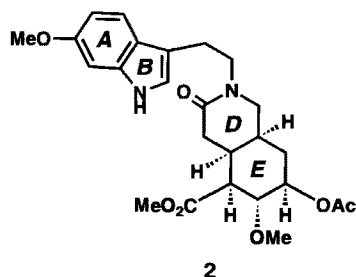
the carboxyl group in **16** with diazomethane gives, after acetylation of the C-3 hydroxyl group and dihydroxylation of the carbon-carbon double bond, intermediate **17**. Oxidative cleavage of the vicinal diol in **17** with periodic acid gives, after concomitant excision of a carbon atom and esterification of the acetic acid side chain with diazomethane, key intermediate **5**. An elegant and efficient solution to the construction of reserpine's E-ring has now been found. At first glance, it may seem as though the stereogenic center adjacent to the aldehyde group in **5** would or should be susceptible to epimerization. However, intermediate **5** is just a functionalized cyclohexane ring,

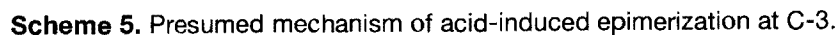
and it adopts the familiar chair conformation wherein four of its five substituents can be oriented equatorially (see Scheme 3). The asymmetric carbon atom next to the aldehyde carbonyl in **5** is thus configurationally stable.

When a solution of intermediate **5** in benzene is treated with 6-methoxytryptamine (**4**), Schiff base intermediate **3** (see Scheme 1) is formed and it is reduced directly with sodium borohydride in methanol to give lactam **2**. In this step, sodium borohydride reduces the imine in **3** to the corresponding secondary amine, which then attacks the proximal acetic ester side chain to give lactam **2**. In practice, the four steps leading from diol **17** to intermediate **2** were performed without the isolation of intermediates. When **2** is treated successively with boiling phosphorus oxychloride and sodium borohydride, (\pm)-methyl-*O*-acetyl-isoreserpate, intermediate **20**, is formed through a cascade of reactions involving intermediates **18** and **19** (Scheme 3). Phosphorus oxychloride accomplishes the conversion of the lactam moiety in **2** into iminochloride **18** which subsequently reacts intramolecularly with the electron-rich indolyl nucleus to give **19**. Reduction of the iminium ion in **19** with methanolic sodium borohydride completes the conversion to **20**.

The relationship between **20** and reserpine (**1**) is close; like reserpine, intermediate **20** possesses the linear chain of all five rings and all six stereocenters. With the exception of the 3,4,5-trimethoxybenzoate grouping, **20** differs from reserpine (**1**) in one very important respect: the orientation of the ring C methine hydrogen at C-3 in **20** with respect to the molecular plane is opposite to that found in reserpine. Intermediate **20** is a reserpate stereoisomer, epimeric at position 3, and its identity was secured by comparison of its infrared spectrum with that of a sample of (–)-methyl-*O*-acetyl-isoreserpate, a derivative of reserpine itself.⁹ Intermediate **20** is produced by the addition of hydride to the more accessible convex face of **19**, and it rests comfortably in a conformation that allows all of the large groups attached to the D/E ring skeleton to be equatorially disposed.

One requirement for the completion of the synthesis of reserpine is that the newly created stereocenter (C-3) at the junction between rings C and D be inverted (Scheme 4). This task could conceivably be achieved simply by treating **20** with acid (see plausible mechanism in Scheme 5). However, at equilibrium, conformer **20a** is expected to be heavily favored over **20b**. In **20a**, the ring E substituents and the large indolyl nucleus are all oriented equatorially, and the prospects for epimerizing the errant stereocenter at position 3 with acid seem grim. If, on the other hand, intermediate **20** could somehow be induced to adopt the alternative and much less stable conformation, **20b**, then there ought to be a substantial thermodynamic driving force for epimerization at position 3; in **20b**, the large indolyl nucleus is axial, and it interacts unfavorably with the two axial substituents (X and Y) in ring E. Thus, if **20** could be locked into conformer **20b**, or one very analogous to it, then in the presence of acid it should undergo, through the cascade of events





presented in Scheme 5, ready isomerization to an even closer relative of reserpine.

An assessment of the structural features in **20** reveals a straightforward and elegant way to accomplish this seemingly formidable task. In **20b**, the acetoxy and carbomethoxy groups are disposed in such a way that it might be possible to achieve the formation of a lactone ring. By freezing the molecular framework into an otherwise unfavorable conformation, this tactic would create a very favorable setting for the desired isomerization reaction. In the event, hydrolysis of both carbomethoxy and acetoxy groups in **20** with potassium hydroxide in methanol, followed by treatment of the resulting hydroxy acid with *N,N'*-dicyclohexylcarbodiimide in pyridine, furnishes (\pm)-isoreserpine acid lactone, intermediate **21**. The lactone ring in **21** enforces the adoption of a conformation wherein the large indolyl group and the E-ring substituents are all axial and are all very close in space. When **21** is exposed to pivalic acid in boiling xylene, it is quantitatively epimerized to (\pm)-reserpine acid lactone, intermediate **22** (see Scheme 5 for presumed mechanism). Cleavage of the lactone ring in **22** with methoxide ion, followed by acylation of the secondary hydroxyl group with 3,4,5-trimethoxybenzoyl chloride in pyridine, gives racemic reserpine [(\pm)-**1**]. By taking advantage of the high crystallinity and low solubility of (–)-reserpine (+)-camphorsulfonate in methanol, racemic reserpine could be readily resolved. The elegant total synthesis of (–)-reserpine (**1**) by the Woodward group is complete.

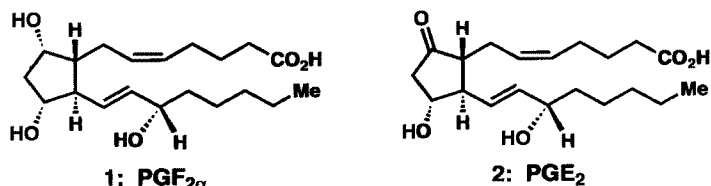
4.4 Conclusion

In this chapter, we have witnessed one of Woodward's most brilliant achievements, and perhaps one of the most remarkable total syntheses of all time. The strategy is brilliant and the tactics even more spectacular. Memorable highlights include the demonstration of the Diels-Alder reaction as an efficient method to construct highly functionalized six-membered rings, the use of a variety of substrate-stereocontrolled reactions by which the various stereocenters can be introduced around the six-membered E ring, and, finally, the ingenious maneuver that enforced the adoption of an unfavorable conformation, thus setting the stage for a facile epimerization.

The Woodward total synthesis of reserpine is an inspirational accomplishment that will, no doubt, remain a classic in the history of total synthesis.¹⁰

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E. J. Corey (1969)

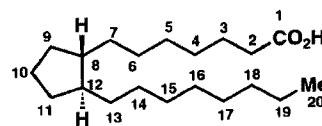
Prostaglandin $F_{2\alpha}$ ($\text{PGF}_{2\alpha}$) and Prostaglandin E_2 (PGE_2)

5.1 Introduction

Using unsaturated fatty acids such as arachidonic acid as biosynthetic building blocks, prostaglandin synthetase assembles a number of structurally homologous hydroxylated compounds which are ubiquitous in mammalian tissues. Collectively known as the prostaglandins, these carbocyclic oxygenated C-20 molecules are hormones that elicit an unusually diverse array of physiological responses.¹ Although virtually all animal tissues contain small quantities of various members of the prostaglandin family, it appears that, in most instances, prostaglandins are biosynthesized on demand from their unsaturated fatty acid precursors. The therapeutic potential of the natural prostaglandins and the challenging task of identifying prostaglandin analogs with selective biological activity have stimulated a substantial multidisciplinary research effort in both academia and industry.²

The prostaglandins were discovered by von Euler in the early 1930s,³ and by 1966, the structures of the first family of prostaglandins were known as a result of the extensive and brilliant investigations of Bergström *et al.*^{3,4} Contained within each member of the prostaglandin family is the C-20 carbon framework of prostanoid acid (**3**) (see Figure 1). The numbering and nomenclature for all the prostaglandins is based on this parent skeleton.

The prostaglandin family comprises several distinct structural types (see Figure 2). The various members of the prostaglandin family are distinguished by the nature of the functionality present in the five-membered ring and by the degree of unsaturation in the



3: prostanoid acid

Figure 1. Parent skeleton of the prostaglandin family.

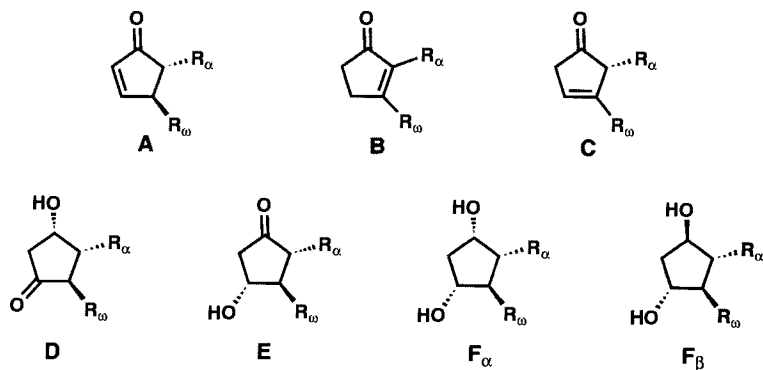
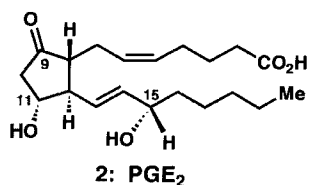
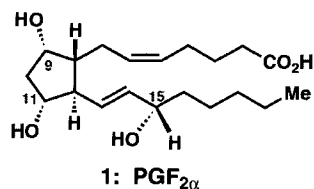


Figure 2. Prostaglandin structural types.



two side-chain appendages. Thus, in the case of $\text{PGF}_{2\alpha}$ (**1**), the two hydroxyl groups affixed to positions 9 and 11 on the cyclopentane ring are characteristic of the F series. The numeral subscript 2 indicates that the side-chain appendages accommodate a total of two carbon-carbon double bonds and the subscript α indicates that the C-9 hydroxyl group is oriented below the plane defined by the saturated five-membered ring. $\text{PGF}_{2\beta}$ is a diastereoisomer of $\text{PGF}_{2\alpha}$ and its C-9 hydroxyl group is oriented above the plane of the five-membered ring; it is epimeric to $\text{PGF}_{2\alpha}$ at C-9. The β -hydroxyketo moiety, the characteristic structural feature of the D and E series of prostaglandins, is particularly unstable in both acidic and basic media. In fact, outside of the pH range 5 to 8, E-type prostaglandins undergo facile dehydration to give A-type prostaglandins.⁵ Further exposure of A-type prostaglandins to base results in isomerization to the more stable B-type prostaglandins through the intermediacy of C-type prostaglandins.

As targets for total synthesis, the prostaglandins present numerous challenges. Members of the F-series possess a total of five asymmetric carbon atoms and four of these are disposed in a consecutive chain in the cyclopentane ring. The task of securing correct relative stereochemical relationships between the stereocenters on the cyclopentane ring is rendered even more formidable by virtue of the fact that five-membered rings do not adopt predictable conformations. Moreover, the hydroxyl-bearing stereocenter at position 15, remote as it is to the contiguous stereocenters in the five-membered ring, presents a special challenge. The prospects for controlling the formation of the C-15 stereocenter by taking advantage of preexisting asymmetry do not seem favorable. In addition, a prerequisite for a total synthesis of the prostaglandins is the development and/or application of complimentary methodology for the stereoselective construction of *cis*- and *trans*-disubstituted olefins. Finally, the difficulties inherent in a projected total synthesis of the E-type prostaglandins must not be overlooked. The pronounced

lability of the β -hydroxyketo moiety in either acidic or basic media affords little latitude with regard to a final deprotection step.

Not since the fruitful era of the β -lactam antibiotics and the steroids had a class of compounds generated so much research activity in organic synthesis. Indeed, the discovery of the prostaglandins as potent pharmaceutical agents and the complex pattern of stereochemistry that characterizes their structures motivated the development of a large number of ingenious strategies and synthetic methods of general utility.⁶ One of the most successful and general strategies for the synthesis of prostaglandins emerged from E. J. Corey's laboratory at Harvard. Corey's elegant and practical strategy for prostaglandin synthesis permits the assembly of the entire prostaglandin family in optically active form from a common precursor. Although Corey's basic strategy was disclosed in 1969,⁷ numerous improvements and modifications of the original strategy have been made in Corey's laboratory and in industry. By virtue of its overall efficiency and because optical resolution can be performed at an early stage, Corey's synthesis has been adapted for pilot-plant production.

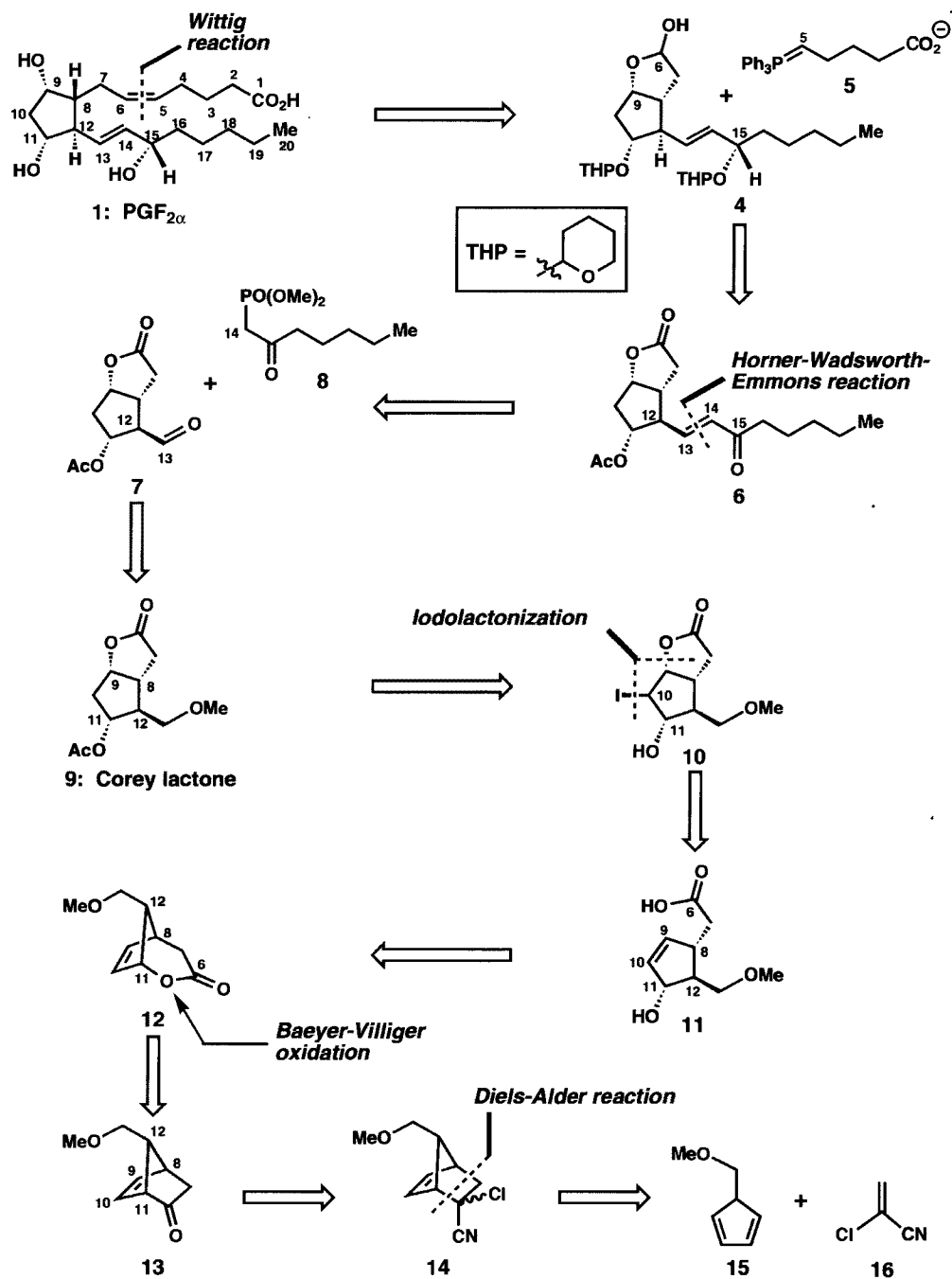
In this chapter, we present Corey's strategy for the synthesis of PGF_{2 α} (**1**) and PGE₂ (**2**). Because a thorough and concise summary of Corey's prostaglandin synthesis including the numerous improvements disclosed up to the mid-1970s has already been published,^{6a} we have opted to address here the original strategy and the more recent refinements which have been reported up to 1992.

5.2 Retrosynthetic Analysis and Strategy

Corey's strategy is commonly referred to as the bicycloheptane approach because it entails the assembly of a substituted bicyclo[2.2.1]heptane ring framework that possesses, in latent form, the functionalized cyclopentane nucleus of the prostaglandins (see Scheme 1). Cleavage of the generic bicycloheptane ring system, in the indicated way, would unveil a substituted five-membered ring with key appendages oriented properly in space. The general features of Corey's strategy are outlined retrosynthetically, for the specific case of PGF_{2 α} (**1**), in Scheme 2.



Scheme 1. Corey's bicycloheptane synthesis strategy.

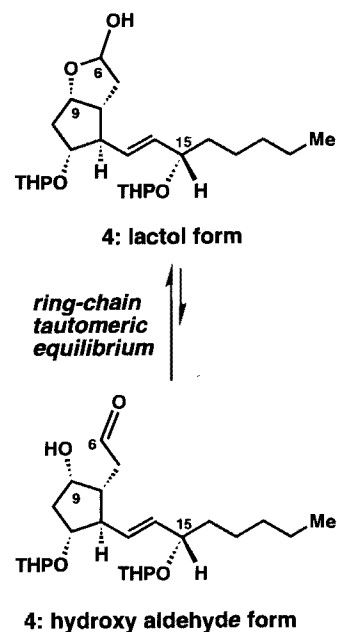


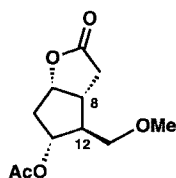
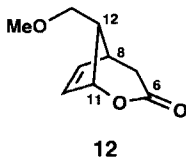
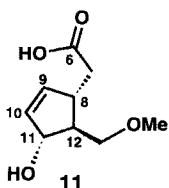
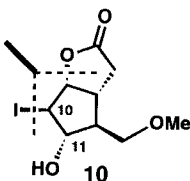
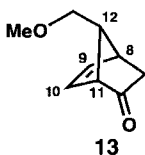
Scheme 2. Retrosynthetic analysis of $PGF_{2\alpha}$ (**1**).

The $\Delta^{5,6}$ double bond in $\text{PGF}_{2\alpha}$ (**1**) provides a convenient opportunity for molecular simplification. Retrosynthetic scission of the *cis* C5–C6 double bond in **1** furnishes lactol **4** and phosphonium ylide **5** as potential precursors. Lactol **4** is an interesting molecule which exists in equilibrium with an isomeric hydroxy aldehyde. Although it is likely that the closed lactol form would be heavily favored at equilibrium, the free aldehyde form of **4**, as scarce as it may be at equilibrium, is reactive and it should participate in a thermodynamically favorable Wittig reaction⁸ in the presence of phosphorous ylide **5**. Thus, by stressing the equilibrium that naturally exists between the closed lactol and hydroxy aldehyde forms of **4** in this way, it ought to be possible to achieve a smooth union of intermediates **4** and **5** to give a protected derivative of **1**. Of course, an important stereochemical issue presents itself here. It is conceivable that the convergent union of intermediates **4** and **5** through a Wittig reaction could occur with little or no preference for a particular olefin stereoisomer. However, on the basis of strong literature precedent,⁸ it was anticipated that a Wittig reaction between the free aldehyde form of **4** and the nonstabilized phosphorous ylide **5** would proceed stereoselectively to give the desired *cis* C5–C6 olefin. Through some conventional functional group manipulations, intermediate **4** could conceivably be derived from enone lactone **6**. As we have already remarked, the stereogenic center at C-15 presents a significant challenge. The introduction of the C-15 stereocenter through a 1,2-reduction of the enone in **6** is very logical and would appear to constitute a viable solution to this problem. The enone carbonyl at C-15 in **6** is, however, situated at such distance from other elements of asymmetry that it may be impossible to control the stereochemical course of the reduction step by exploiting pre-existing chirality in the substrate. Although an ingenious substrate-stereocontrolled enone reduction process was eventually developed in Corey's group,⁹ it was recently discovered by Corey that a catalytic asymmetric reduction protocol can accomplish a highly stereoselective reduction of a C-15 enone carbonyl (*vide infra*). Suffice it to say, an efficient method now exists which is equal to the task of establishing the (15*S*) stereocenter in the prostaglandins through a straightforward reduction of a C-15 enone carbonyl group.

Retrosynthetic cleavage of the $\Delta^{13,14}$ double bond in **6** significantly simplifies the side-chain appendage attached to C-12 and affords aldehyde **7** and ketophosphonate **8** as potential precursors. In the synthetic direction, a Horner–Wadsworth–Emmons reaction¹⁰ would appear to provide a very simple means of joining intermediates **7** and **8** with concomitant formation of the requisite *trans* C13–C14 olefin. Retrosynthetic simplification of aldehyde **7** provides intermediate **9**, a molecular assembly commonly known as the *Corey lactone*.

The retrosynthetic maneuvers that we have addressed thus far have only resulted in simplification of the vicinal side-chain substituents appended to carbons 8 and 12; we have yet to address the marked stereochemical complexity of the cyclopentane nucleus of



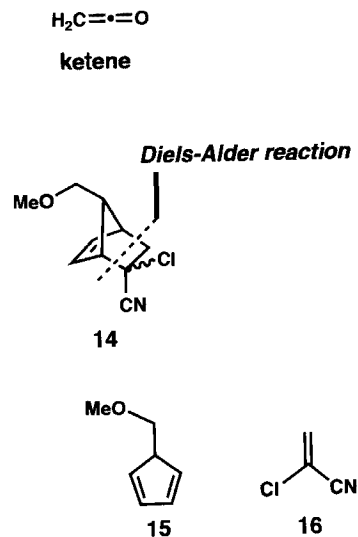
**9: Corey lactone****Iodolactonization****12****13**

PGF_{2α}. The cyclopentane ring of the Corey lactone (**9**) is the host of four contiguous stereogenic centers. Retrosynthetic “simplification” of **9** provides **10**, a construct which is more complex than **9**! Nevertheless, intermediate **10** possesses structural features that satisfy the requirement for the iodolactonization transform. The iodolactone in **10** constitutes the retron for the iodolactonization transform.¹¹ Cleavage of the indicated bonds in **10** sacrifices two of the five stereocenters and provides unsaturated carboxylic acid **11** as a retrosynthetic precursor. A most useful consequence of the close spatial relationship between the carboxyl group and the C9–C10 double bond in **11** is that it should be possible to create, through iodolactonization,¹² the key oxygen-bearing stereocenter at C-9. In the event, iodine would be expected to engage the C9–C10 double bond diastereoface in **11** opposite to the acetic acid side chain. The iodonium ion intermediate thus formed would then elicit an intramolecular attack by the carboxyl group to give intermediate **10**. The stereoelectronic preference for a *trans* addition across the alkene and the strong inherent preference for the formation of a *cis*-fused bicyclo[3.3.0]octane framework would guide the assembly of **10**. Thus, the iodolactonization reaction could allow stereochemistry to be communicated from the stereocenter already present at C-8 to C-9.¹³ Acetylation of the C-11 hydroxyl group, followed by reductive removal of the iodine atom in **10**, would then complete the synthesis of the Corey lactone (**9**).

To clarify the relationship between intermediate **11** and its predecessor, intermediate **12**, it is instructive to recognize the correspondence between the C-11 hydroxyl group and the C-6 carboxyl group in **11**. Thus, even though the structural relationship between intermediates **11** and **12** may not appear to be close, subjecting **12** to a straightforward lactone hydrolysis reaction could furnish hydroxy acid **11**. An elegant feature of Corey’s design is the recognition that lactone **12**, with its key oxygen-bearing stereocenter at C-11, could be formed in a single step from bicyclo[2.2.1]heptenone **13** through a Baeyer–Villiger oxidation.¹⁴ The Baeyer–Villiger oxidation can accomplish the conversion of cyclic ketones to lactones with concomitant expansion of the ring by one atom. If an unsymmetrical cyclic ketone is employed in a Baeyer–Villiger reaction (i.e. ketone **13**), an oxygen atom is inserted regioselectively between the carbonyl group and the more electron-releasing site (usually the more substituted site). If the migrating carbon is unsymmetrically substituted, stereochemistry is retained in the oxidation process. As a tool in organic synthesis, the Baeyer–Villiger oxidation is very valuable because it is stereospecific and frequently highly regioselective.

Bicyclic ketone **13** is a pivotal intermediate in Corey’s approach to the prostaglandins. Buried within **13** is the five-membered ring of PGF_{2α}, albeit in an undeveloped form. It would appear that a particularly direct approach to the synthesis of **13** would involve a [4+2] cycloaddition reaction between substituted cyclopentadiene **15** and ketene. Unfortunately, however, ketene itself is not a suit-

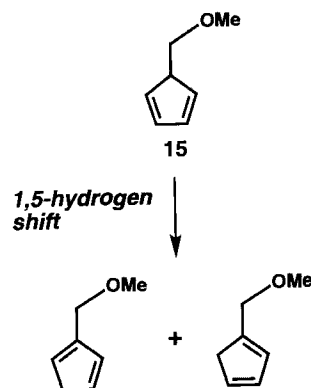
able dienophile in Diels–Alder reactions. Ketene instead participates in [2+2] cycloaddition reactions with 1,3-dienes to give functionalized cyclobutanones. Thus, the development and use of reagents that are *synthetically equivalent* to ketene as dienophiles in [4+2] cycloaddition reactions constitutes an important advance in organic synthesis.¹⁵ One such ketene equivalent is 2-chloroacrylonitrile (**16**). Numerous successful applications of 2-chloroacrylonitrile as the dienophilic component in Diels–Alder reactions and the straightforward conversion of the chloronitrile adduct into the corresponding unsaturated ketone through basic hydrolysis attest to the value of **16** as a ketene equivalent in [4+2] cycloaddition reactions.¹⁵ Ketone **13** could thus be derived, retrosynthetically, from chloronitrile **14**. In the synthetic direction, exposure of **14** to aqueous potassium hydroxide could accomplish its hydrolysis to give ketone **13**.¹⁶ Intermediate **14** could be formed in one step through a Diels–Alder reaction^{15b,c} between the 5-substituted cyclopentadiene **15** and commercially available 2-chloroacrylonitrile (**16**).

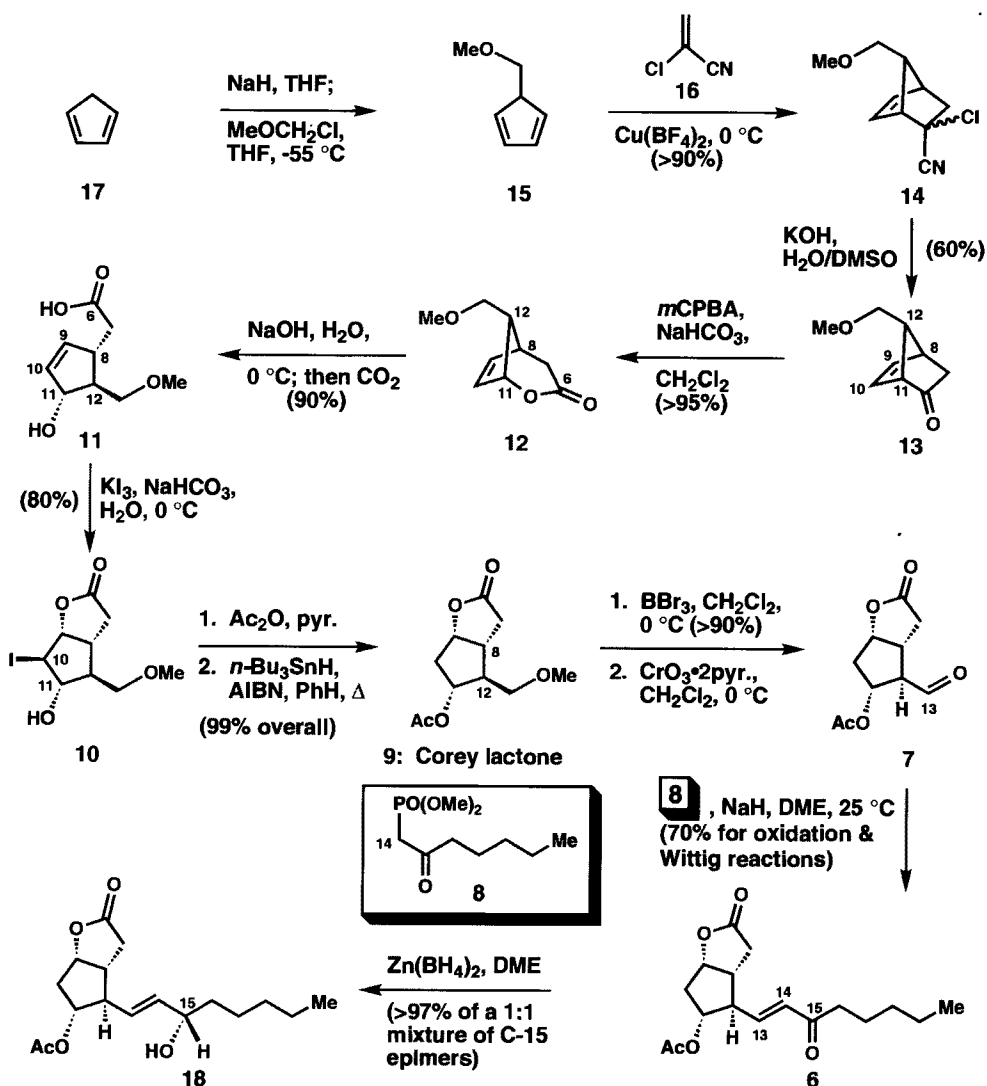


5.3 Total Synthesis

Corey's original prostaglandin synthesis commences with the alkylation of cyclopentadienylsodium, derived from the action of sodium hydride on cyclopentadiene (**17**), with chloromethyl methyl ether (MOMCl) in THF at -55°C to give 5-methoxymethyl-1,3-cyclopentadiene (**15**) (see Scheme 3). Intermediate **15** is itself a rather unstable substance. Under acidic or basic conditions and even at temperatures as low as 0°C , **15** readily undergoes a 1,5-hydrogen shift to give isomeric 1- and 2-substituted cyclopentadienes. To compensate for the instability of **15**, it was found necessary to remove the solvent below 0°C and to use crude **15** immediately. Intermediate **15** is to serve as the 4π component in a Diels–Alder reaction with the ketene equivalent 2-chloroacrylonitrile (**16**). Treatment of freshly prepared **15** with **16** in the presence of a catalytic amount of cupric tetrafluoroborate at 0°C results in smooth [4+2] cycloaddition to give **14** as a racemic mixture of epimeric chloronitriles in a yield exceeding 90%. The powerful Lewis acid, cupric tetrafluoroborate, is an essential additive because it accelerates the rate of the Diels–Alder reaction between **15** and **16** and it allows the reaction to be performed at 0°C . If the union of intermediates **15** and **16** required thermal assistance, it is very likely that diene **15** would undergo isomerization prior to cycloaddition.

The action of aqueous potassium hydroxide on chloronitrile **14** in DMSO at 25 – 30°C accomplishes the hydrolysis of the chloronitrile moiety and furnishes ketone **13** in a yield of 80%. Treatment of a solution of ketone **13** in CH_2Cl_2 with *m*CPBA and sodium bicarbonate results in a selective Baeyer–Villiger oxidation to give bicyclic lactone **12** in $>95\%$ yield. It is noteworthy that the Baeyer–Villiger oxidation is completely regioselective and that the





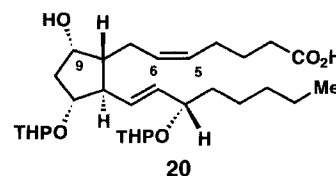
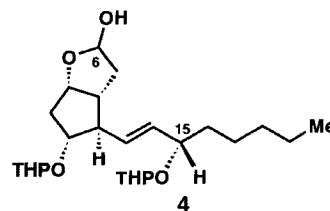
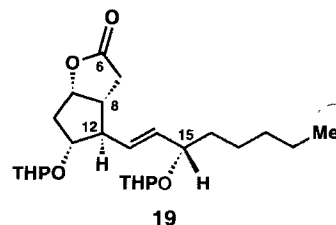
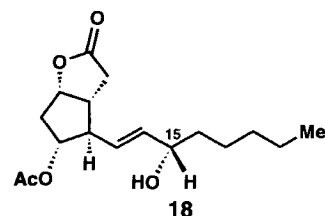
Scheme 3. Synthesis of intermediate 18.

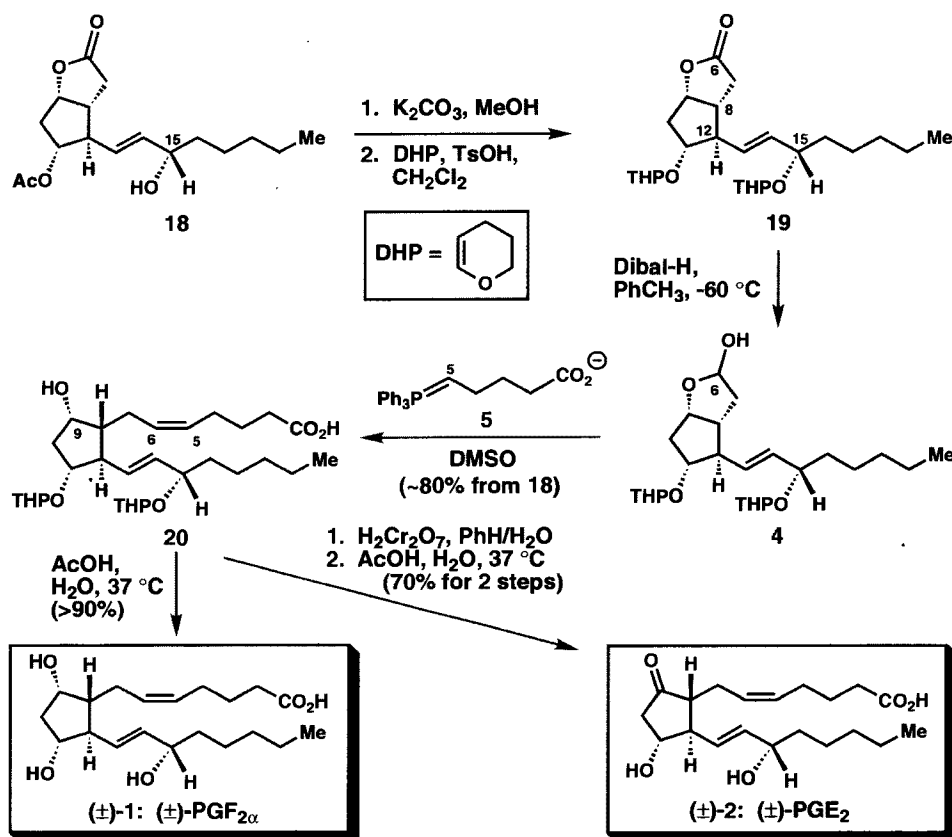
disubstituted C9–C10 double bond (PG numbering) is not epoxidized under these conditions. Saponification of the lactone ring in **12** with aqueous sodium hydroxide at 0°C, followed by neutralization of the reaction mixture with carbon dioxide, provides hydroxy acid **11** which is directly subjected to iodolactonization¹² with aqueous potassium triiodide solution to give the crystalline iodolactone **10** in 72% overall yield. Acetylation of the C-11 secondary hydroxyl group in **10** with acetic anhydride, followed by reductive cleavage of the carbon–iodine bond with tri-*n*-butyltin hydride and a catalytic amount of azobisisobutyronitrile (AIBN), provides intermediate **9**, the Corey lactone, in 99% overall yield.

With the four requisite stereocenters embedded within its cyclopentane ring, intermediate **9** must now be converted into a form that can accommodate the introduction of the side-chain appendages at carbons 8 and 12. Cleavage of the methyl ether in **9** with boron tribromide affords a primary alcohol (>90%), which is oxidized with Collins reagent to give aldehyde **7**. The instability of **7** required that it be taken forward immediately in crude form. Horner–Wadsworth–Emmons reaction^{8d,10} between aldehyde **7** and the sodium salt of dimethyl-2-oxoheptylphosphonate (**8**) in 1,2-dimethoxyethane at 25°C provides enone lactone **6** in 70% overall yield from the primary alcohol. Intermediate **6** possesses all of the carbon atoms of the lower side chain of PGF_{2α} and it is noteworthy that the desired *trans* C13–C14 double bond is formed in a completely stereoselective fashion in the olefination step. A chemoselective reduction of the C-15 enone carbonyl in **6** with zinc borohydride provides an equimolar mixture of diastereomeric allylic alcohols, epimeric at C-15, in >97% yield. Intermediate **18** is obtained in diastereomerically pure form after preparative thin-layer chromatography. The undesired 15β epimer can be oxidized to enone **6** with activated MnO₂ and recycled. Solvolysis of the acetate in **18** with basic methanol affords a diol which is smoothly converted into the bistetrahydropyranyl derivative **19** with excess dihydropyran and a catalytic amount of *para*-toluenesulfonic acid (see Scheme 4).

With the ω side chain at C-12 in place, we are now in a position to address the elaboration of the side chain appended to C-8 and the completion of the syntheses. Treatment of lactone **19** with diisobutylaluminum hydride (Dibal-H) accomplishes partial reduction of the C-6 lactone carbonyl and provides lactol **4**. Wittig condensation⁸ of **4** with nonstabilized phosphorous ylide **5** proceeds smoothly and stereoselectively to give intermediate **20**, the bistetrahydropyranyl ether of (±)-**1**, in a yield of ~80% from **18**. The convergent coupling of compounds **4** and **5** is attended by the completely selective formation of the desired *cis* C5–C6 olefin.

Compound **20** is a key intermediate, for it is the precursor to both PGF_{2α} and PGE₂. Hydrolytic removal of the tetrahydropyranyl protecting groups from (±)-**20** under mild conditions with aqueous acetic acid provides racemic PGF_{2α} (**1**) in >90% yield. Alternatively, a mild chromic acid oxidation of the C-9 secondary hydroxyl group in **20** to the corresponding ketone, followed by cleavage of





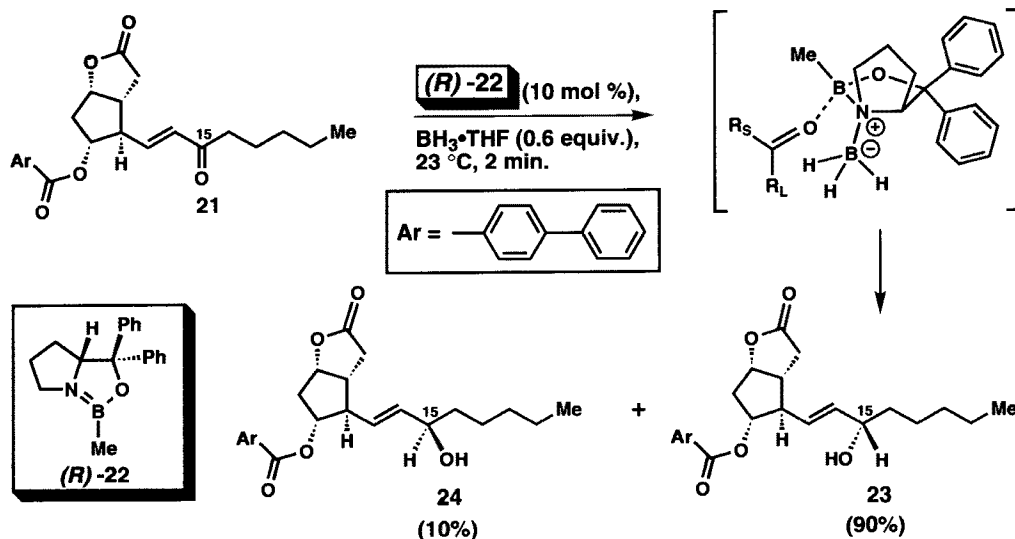
Scheme 4. Synthesis of (±)- $\text{PGF}_{2\alpha}$ [(±)-1] and (±)- PGE_2 [(±)-2].

the tetrahydropyranyl protecting groups, again with aqueous acetic acid, furnishes racemic PGE_2 (2) in an overall yield of 70 %.

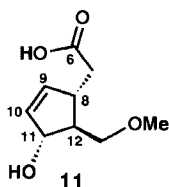
During the latter half of the 1980s, some very successful catalysts were developed by the Corey group for the purpose of controlling the absolute stereochemical course of several fundamental reaction types.¹⁷ Carbonyl reductions,¹⁸ Diels–Alder reactions,¹⁹ aldol condensations,²⁰ carbonyl allylations,²¹ and Claisen rearrangements²² can all be carried out efficiently and enantioselectively under the influence of one of Corey's catalysts. In 1987, Corey's group disclosed numerous examples of remarkably efficient and enantioselective reductions of unsaturated ketones to give the corresponding unsaturated alcohols using borane and an enantiomerically pure oxazaborolidine catalyst.^{18b} Among these exciting examples was an enantioselective reduction of an important intermediate

in Corey's prostaglandin synthesis (see Scheme 5). Treatment of the enone **21**⁹ with 0.6 equivalents of borane in THF at 23 °C for two minutes in the presence of 10 mole % of Corey's oxazaborolidine catalyst (*R*)-**22** provides a 90:10 mixture of the (15*S*) alcohol **23** and the (15*R*) diastereoisomer **24**. In the presence of (*S*)-**22** and under the same reaction conditions, enone **21** is again reduced in a stereoselective fashion to give a 91:9 ratio of allylic alcohol diastereoisomers in favor of the (15*R*) alcohol **24**. Changing the handedness of the oxazaborolidine catalyst changes the preferred stereochemical course of the ketone reduction. It would appear that the long-standing problem of defining the stereocenter at C-15 in prostaglandin synthesis finds a most elegant and practical solution in Corey's catalytic asymmetric ketone reduction protocol.

A key transformation in Corey's prostaglandin synthesis is a Diels–Alder reaction between a 5-(alkoxymethyl)-1,3-cyclopentadiene and a ketene equivalent such as 2-chloroacrylonitrile (**16**). As we have already witnessed in Scheme 3, it is possible to bring about a smooth [4+2] cycloaddition reaction between 5-substituted cyclopentadiene **15** and 2-chloroacrylonitrile (**16**) to give racemic **14** as a mixture of epimeric chloronitriles. Under these conditions, the diastereomeric chloronitriles are both produced in racemic form because one enantiotopic face of dienophile **16** will participate in a Diels–Alder reaction with the same facility as the other enantiotopic face. In subsequent work, Corey's group demonstrated that racemic hydroxy acid **11**, derived in three steps from racemic **14** (see Scheme 3), could be resolved in a classical fashion with (+)-ephe-



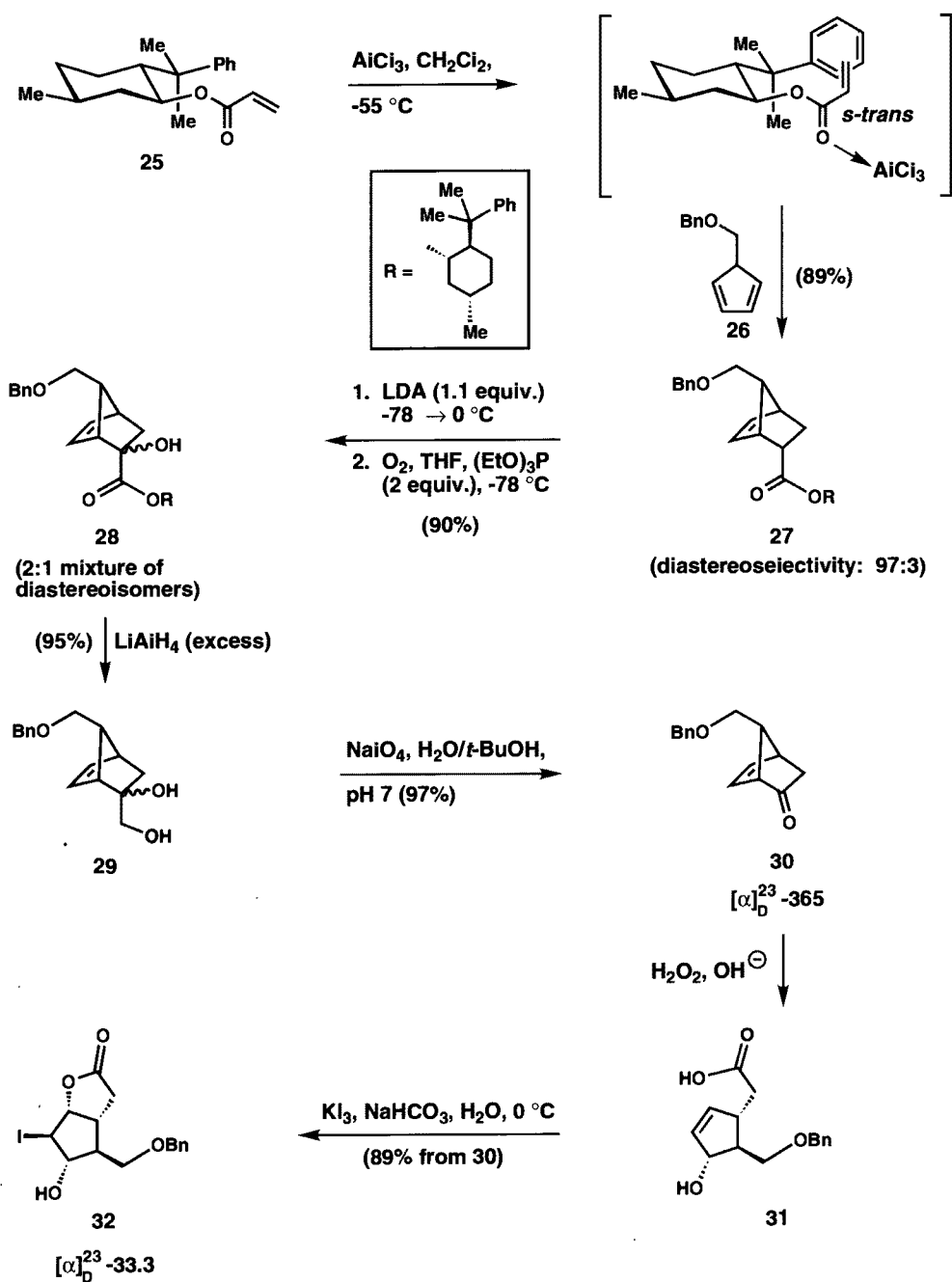
Scheme 5. Corey's diastereoselective catalytic reduction of ketone **21**.



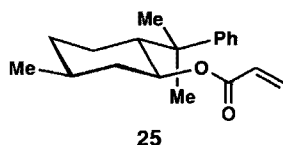
drine.^{7b} After acid treatment, **11** could be obtained in enantiomerically pure form so that optically active prostaglandins could be prepared. Of course, if the objective is to prepare prostaglandins in enantiomerically pure form, a flaw inherent in a strategy such as this is that 50% of the material obtained by synthesis is wasted! On the other hand, an elegant and practical solution to the problem of preparing the natural prostaglandins could be realized if the initial Diels–Alder step could be induced to proceed enantioselectively. Such an approach was forthcoming.

In 1975, the Corey group disclosed that enantiomerically pure bicyclo[2.2.1]heptenone **30**, prepared in a few steps from an asymmetric Diels–Alder reaction, could be transformed into enantiomerically pure iodolactone **32** (see Scheme 6).²³ In the event, treatment of a solution of enantiomerically pure acrylate **25** and aluminum chloride in methylene chloride at -55°C with 5-(benzyloxymethyl)-1,3-cyclopentadiene **26** affords, through an asymmetric Diels–Alder reaction,²⁴ *endo* adduct **27** in 89% yield. It is assumed that coordination of the acrylate ester carbonyl in **25** with aluminum trichloride favors the adoption of an *s-trans* conformation and that the proximal aromatic ring confers stability to the electron-deficient carbonyl carbon in both the complex and the transition state. π -Facial selectivity in the Diels–Alder reaction with diene **26** is then a consequence of steric screening of one of the two diastereotopic faces of the dienophile. Exposure of the ester enolate derived from the action of lithium diisopropylamide (LDA) on **27** to an oxygenated solution of THF containing two equivalents of triethylphosphite results in the formation of **28** as a 2:1 mixture of *exo*- and *endo*-hydroxyl diastereoisomers. Triethylphosphite is used to reduce the mixture of α -hydroperoxy esters that forms initially in this reaction. Reductive removal of the 8-phenylmenthyl chiral auxiliary with lithium aluminum hydride affords **29** as a mixture of *exo* and *endo* diols, and it is important to note that the 8-phenylmenthol could be recovered for reuse. The production of **29** as a mixture of diastereoisomers is inconsequential because both diol stereoisomers are converted smoothly into optically active bicyclic ketone **30** in the presence of sodium metaperiodate. Exposure of ketone **30** to basic hydrogen peroxide accomplishes, in one step, the crucial Baeyer–Villiger oxidation to the corresponding lactone and the hydrolytic cleavage of the lactone ring to give the acid-sensitive hydroxy acid **31**. Direct treatment of **31** with potassium triiodide in aqueous NaHCO_3 at 0°C induces iodolactonization and provides iodolactone **32** in enantiomerically pure form (89% from **30**).

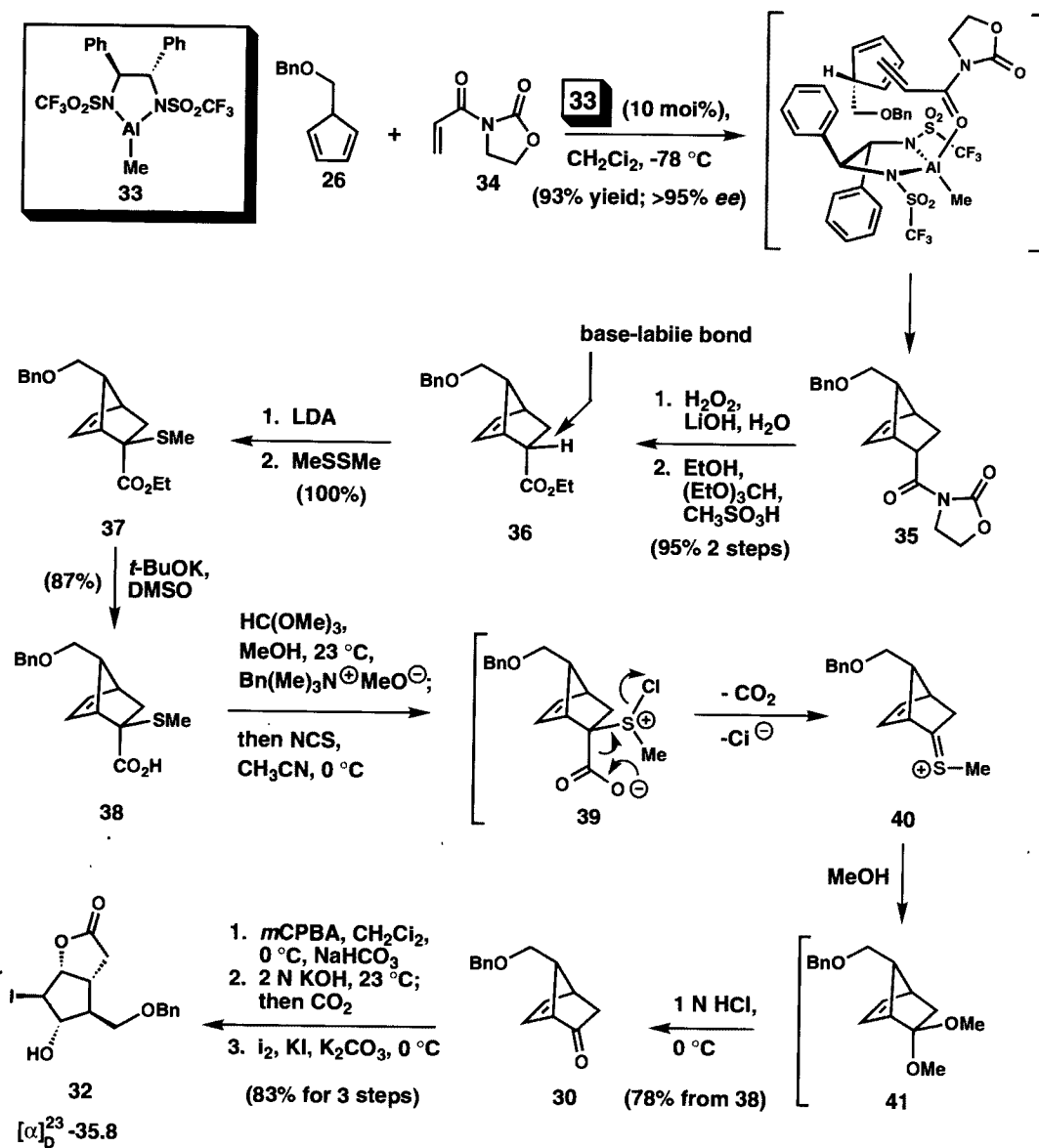
Although the successful asymmetric Diels–Alder based strategy outlined in Scheme 6 would appear to provide a practical route to optically active prostaglandins, an even more impressive advance in the evolution of Corey's prostaglandin synthesis was reported in 1991. On the basis of exciting precedent established previously in Corey's group,^{19a} it was anticipated that a catalytic quantity of the C₂-symmetric aluminum-containing chiral ligand **33** could bring

**Scheme 6.** Asymmetric Diels-Alder approach to enantiomerically pure iodolactone **32**.

about an enantioselective union of 5-(benzyloxymethyl)-1,3-cyclopentadiene **26** and 3-acrylyl-1,3-oxazolidin-2-one **34** through a Diels–Alder reaction (see Scheme 7). Indeed, in the presence of 10 mole % of the (*S,S*)-catalyst **33**, achiral diene **26** and achiral dienophile **34** combine smoothly and enantioselectively in methylene chloride at -78°C to give Diels–Alder adduct **35** in an excellent yield of 93 % ($>95\%$ *ee*).^{19b} The chiral, C₂-symmetric bissulfonamide used to prepare catalyst **33** is recovered easily from the reaction mixture. The action of aqueous lithium hydroxide/hydrogen peroxide²⁵ on **35** accomplishes hydrolysis of the imide to give the corresponding acid in quantitative yield. Fischer esterification of this substance with ethanol, triethyl orthoformate, and methanesulfonic acid provides ethyl ester **36** in 95 % yield. By virtue of its disposition relative to the electron-withdrawing ester carbonyl group, the indicated carbon–hydrogen bond in **36** is labile, and, in the presence of LDA, a smooth deprotonation reaction takes place to give an ester enolate. Although this enolate possesses nucleophilic potential at oxygen and at the α -carbon (i.e. an ambident nucleophile), it reacts regio- and stereoselectively with MeSSMe on carbon to give intermediate **37** in quantitative yield. Treatment of ethyl ester **37** with potassium *tert*-butoxide in DMSO affords, in 87 % yield, carboxylic acid **38**, a suitable substrate for an oxidative decarboxylation reaction. In the presence of *N*-chlorosuccinimide (NCS), the thiomethyl sulfur atom is chlorinated to give chlorosulfonium ion **39** as a transient intermediate.²⁶ This reactive species provides the impetus for a spontaneous decarboxylation reaction leading to the formation of a new sulfonium ion **40**. Rapid solvolysis of sulfonium ion **40** with methanol then furnishes dimethylketal **41**, a substance which undergoes ready hydrolysis to the desired, enantiomerically pure bicyclic ketone **30** upon treatment with 1 *N* aqueous HCl (78 % yield from **38**). Finally, Baeyer–Villiger oxidation of **30**, followed sequentially by lactone hydrolysis and iodolactonization reactions, provides, after recrystallization, enantiomerically pure iodolactone **32** in an overall yield of 83 % from **30**.

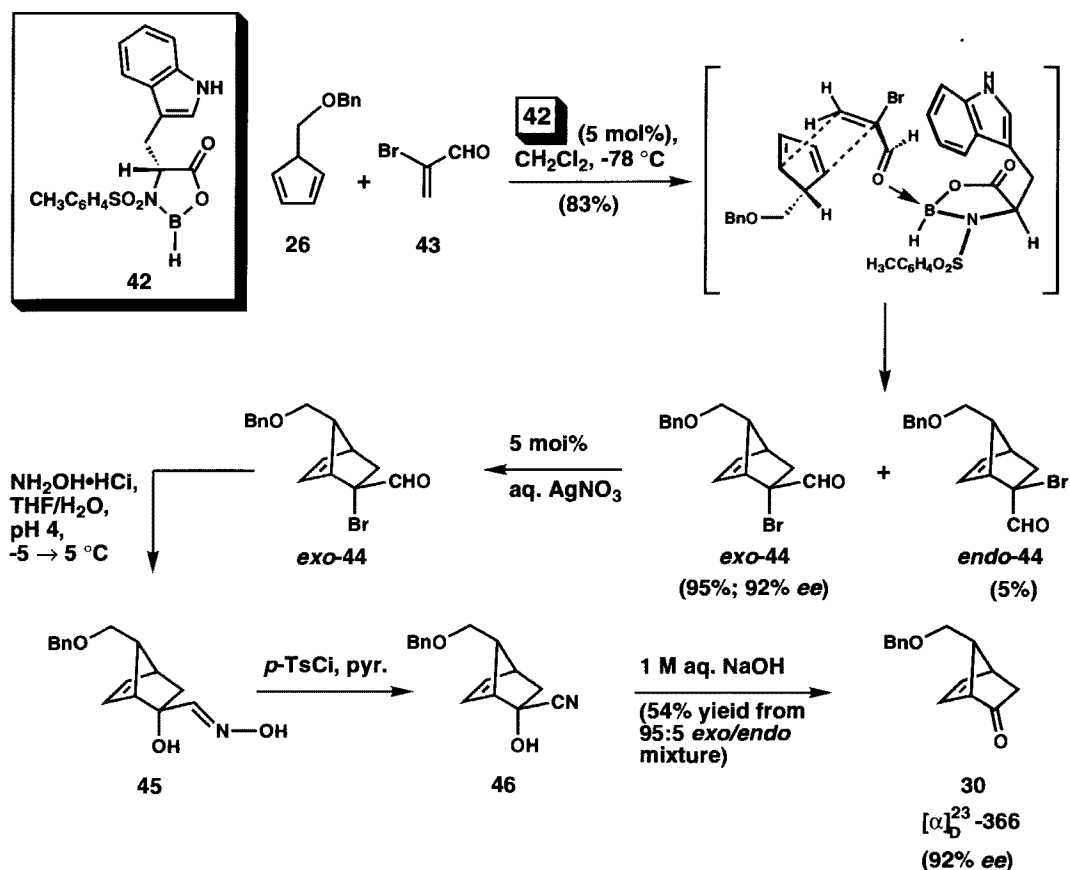


The discovery that the 8-phenylmenthyl group is an effective chiral auxiliary for Diels–Alder reactions of acrylate esters stands as an event of some historical significance (see Scheme 6). In particular, the observation that the acrylate ester of 8-phenylmenthol **25** reacts with cyclopentadiene (AlCl₃ catalysis) in a manner that is significantly more stereoselective than the reaction between the acrylate ester of (–)-menthol (i.e. intermediate **25** with H in place of phenyl) and cyclopentadiene (SnCl₄ catalysis)^{19a,23} suggests that the aromatic ring in **25** plays a very important role in the cycloaddition reaction. This observation provided the foundation for the idea that “neighboring aromatic π -groups could influence transition state energies in such a way as to enforce high stereoselectivity.”²⁷ Armed with this precedent, Corey’s group discovered and disclosed the preparation and use of yet another extremely successful catalyst for the purpose of conducting catalytic asymmetric Diels–Alder reactions.^{19d,f}



Scheme 7. Catalytic asymmetric Diels–Alder approach to enantiomerically pure iodolactone **32**.

An expedient and stereoselective synthesis of bicyclic ketone **30** exemplifies the utility and elegance of Corey's new catalytic system (see Scheme 8). Reaction of the (*R*)-tryptophan-derived oxazaborolidine **42** (5 mol %), 5-(benzyloxymethyl)-1,3-cyclopentadiene **26**, and 2-bromoacrolein (**43**) at -78°C in methylene chloride gives, after eight hours, diastereomeric adducts **44** in a yield of 83% (95:5 *exo:endo* diastereoselectivity; 96:4 enantioselectivity for the *exo* isomer). After reaction, the *N*-tosyltryptophan can be recovered for reuse. The basic premise is that oxazaborolidine **42** induces the Diels–Alder reaction between intermediates **26** and **43** to proceed through a transition state geometry that maximizes attractive donor–acceptor interactions. Coordination of the dienophile at the face of boron that is *cis* to the 3-indolylmethyl substituent is thus favored.^{19d,f} Treatment of the 95:5 mixture of *exo/endo* diastereomers with 5 mol % aqueous AgNO₃ selectively converts the minor, but more reactive, *endo* aldehyde diastereomer into water-soluble



Scheme 8. Catalytic asymmetric Diels–Alder approach to ketone **30**.

products, and provides the *exo* aldehyde adduct **44** in pure form. Treatment of hydroxy oxime **45**, derived in one step from the action of hydroxylamine hydrochloride on *exo*-**44**, with *para*-toluenesulfonyl chloride and pyridine affords cyanohydrin **46**. In the presence of 1 N aqueous sodium hydroxide, **46** is readily transformed into optically active ketone **30**, a key intermediate for prostaglandin synthesis.

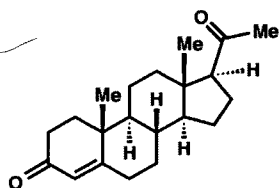
5.4 Conclusion

It was in 1969 when Corey disclosed his elegant and versatile bicycloheptane prostaglandin synthetic strategy. Over the course of the ensuing two and a half decades, Corey's original strategy has evolved in a manner that closely parallels the development of the science of organic synthesis. In fact, it may actually be more appropriate to state that Corey's masterful achievements in the prostaglandin field have contributed many impressive developments in organic synthesis, particularly with respect to catalytic asymmetric synthesis.

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1: progesterone

W. S. Johnson (1971)

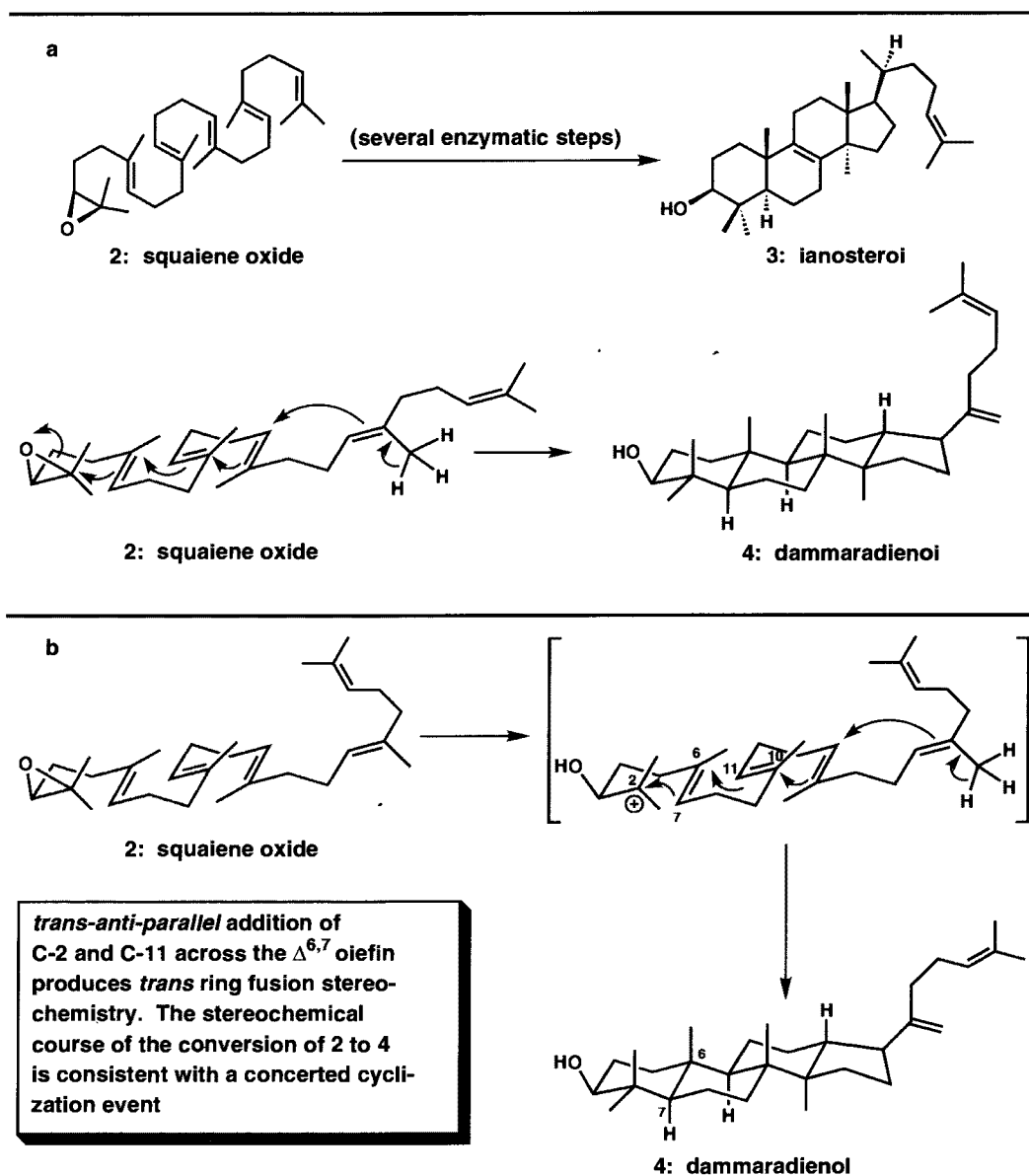
Progesterone

6.1 Introduction

A popular approach to the synthesis of the linearly fused cyclohexanoid frameworks characteristic of the ubiquitous steroids and polycyclic triterpenoids has involved multistep annulations wherein each new six-membered ring is built onto a preexisting ring in a stepwise fashion.¹ The Robinson annulation and the successful annulation methods developed by G. Stork and his group at Columbia have figured prominently in the application of this strategy to the synthesis of numerous polycyclic natural products. In marked contrast to this controlled, stepwise approach to the synthesis of polycyclic natural products, the biomimetic approach can fashion a complex polycyclic array in a single step through a stereospecific cyclization of an appropriately constituted polyunsaturated chain.²

The biomimetic approach to total synthesis draws inspiration from the enzyme-catalyzed conversion of squalene oxide (**2**) to lanosterol (**3**) (through polyolefinic cyclization and subsequent rearrangement), a biosynthetic precursor of cholesterol, and the related conversion of squalene oxide (**2**) to the plant triterpenoid dammaradienol (**4**) (see Scheme 1a).³ The dramatic productivity of these enzyme-mediated transformations is obvious; in one impressive step, squalene oxide (**2**), a molecule harboring only a single asymmetric carbon atom, is converted into a stereochemically complex polycyclic framework in a manner that is stereospecific. In both cases, four carbocyclic rings are created at the expense of a single oxirane ring.

An additional impetus for the development of biomimetic polyolefinic cyclizations was provided by the historically significant Stork–Eschenmoser hypothesis,⁴ a postulate that rationalizes the



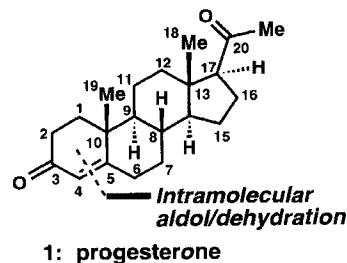
Scheme 1. Enzyme-induced cyclizations of squalene oxide (2) (a) and the Stork–Eschenmoser hypothesis (b).

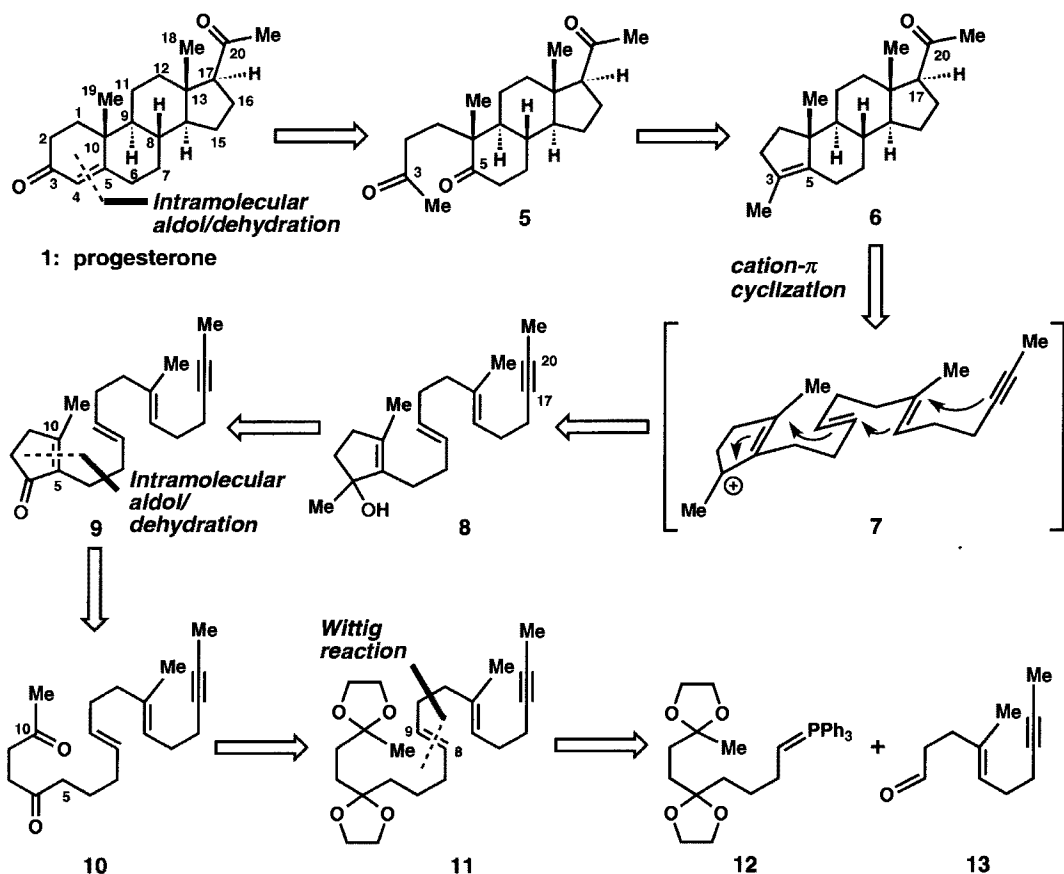
stereochemical course of the biochemical cyclization of squalene oxide on stereoelectronic grounds. In 1955, Stork and Eschenmoser independently proposed that polyunsaturated molecules with *trans* olefinic linkages, such as squalene oxide (**2**), should exhibit an inherent preference for cyclizing in a stereospecific fashion to give a polycyclic molecule which possesses *trans,anti,trans* ring fusion stereochemistry. The important features of the Stork–Eschenmoser hypothesis can be illustrated by using the cyclization of squalene oxide (**2**) to dammaradienol (**4**) as an example (see Scheme 1b). We will assume that protonation of the oxygen of squalene oxide induces opening of the oxirane ring to give a transient tertiary carbonium ion at C-2. Once formed, this electrophilic species would find itself in proximity to the C6–C7 *trans* olefinic linkage and, in such a setting, it is conceivable that this cation could initiate an electrophilic attack upon the $\Delta^{6,7}$ double bond. A Markovnikov addition of a C-2 cation to the proximal $\Delta^{6,7}$ double bond would result in the formation of a σ bond between C-2 and C-7, and the creation of a carbocation at C-6 which could initiate an electrophilic attack upon the C10–C11 *trans* olefin, and so on. According to the Stork–Eschenmoser hypothesis, the addition of the C-2 cation and C-11 to the $\Delta^{6,7}$ double bond occurs in an antiparallel fashion and is analogous to the stereospecific *trans* addition of bromine to alkenes. This elegant hypothesis explains how the all-*trans* stereochemistry of the olefinic bonds in squalene oxide is translated into the *trans,anti,trans* ring fusion stereochemistry characteristic of polycyclic triterpenes such as **4**. A corollary to the Stork–Eschenmoser hypothesis is that a *cis* double bond will lead to the formation of a *cis*-fused ring system.

Unambiguous experimental support for the Stork–Eschenmoser hypothesis was provided by W. S. Johnson's group at Stanford during the early stages of a brilliant research program directed toward the development of biomimetic polyolefinic cyclizations into viable synthetic strategies.^{2a–c,5} In this chapter, we will address Johnson's elegant synthesis of progesterone (**1**),⁶ a hormone that prepares the lining of the uterus for implantation of an ovum.

6.2 Retrosynthetic Analysis and Strategy

The general features of this synthesis are outlined retrosynthetically in Scheme 2. The enone of progesterone (**1**) can be regarded as the retron for the intramolecular aldol/dehydration transform;⁷ retrosynthetic scission of the C4–C5 double bond (steroid numbering) furnishes intermediate **5**, and it is important to recognize that a simple aldol cyclodehydration maneuver could convert **5** into progesterone. Triketone **5**, containing as it does two ketone carbonyls in a 1,5 relationship, could conceivably be derived in one step from intermediate **6** through oxidative cleavage of the $\Delta^{3,5}$ tetrasubsti-





Scheme 2a. Retrosynthetic analysis of progesterone (1).

tuted double bond. Substituted cyclopentene rings, like the one present in **6**, are useful progenitors for cyclohexenones; the combination of oxidative cleavage and aldol cyclodehydration reactions can accomplish the conversion of a methyl substituted cyclopentene nucleus into a cyclohexenone.

The retrosynthetic operations that we have addressed thus far have not resulted in significant structural simplification. After all, intermediate **6** still possesses a linear fusion of four rings and six contiguous asymmetric carbon atoms. But, nevertheless, intermediate **6** could potentially be derived in one step from intermediate **8**, a polyunsaturated monocyclic compound containing only one stereogenic center. Under conditions that would be conducive to a heterolytic cleavage of the C–OH bond in **8**, it is conceivable that the resultant tertiary allylic carbonium ion **7** would participate in a

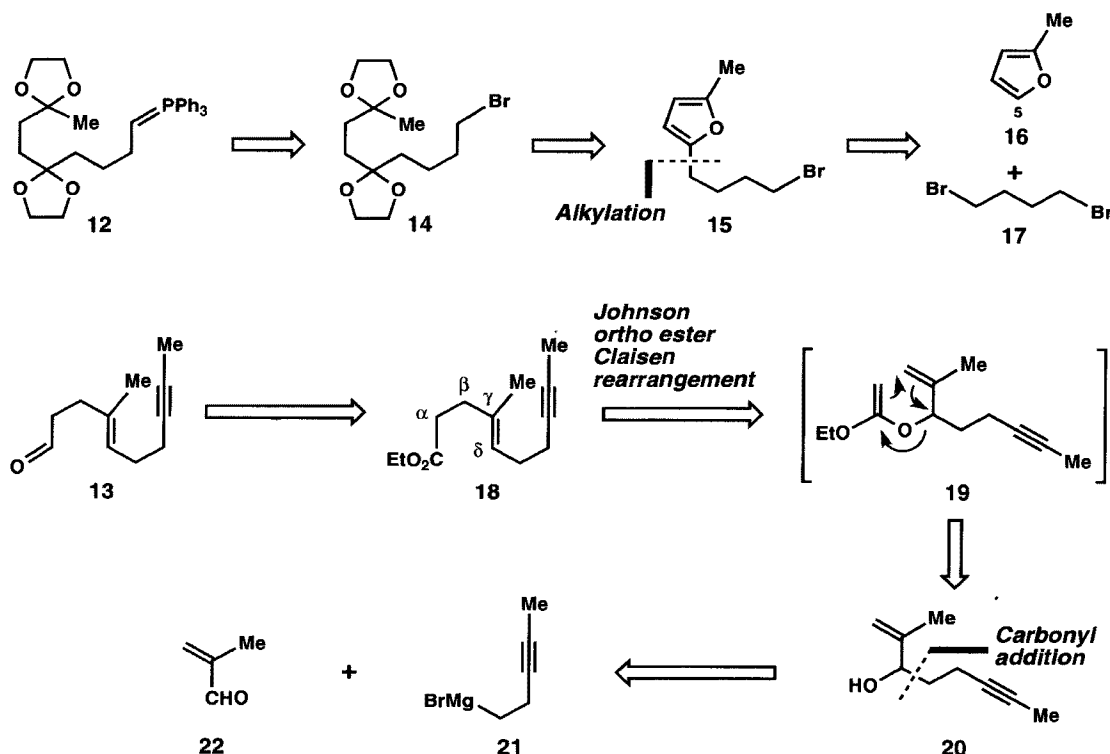
polyolefinic cyclization reaction to give, after workup, intermediate **6**. At one fell swoop, three rings and six contiguous stereogenic centers could be created! Tertiary carbinol **8** could be fashioned from enone **9** through a straightforward carbonyl addition reaction.

We are once again faced with the challenge of constructing a cyclic enone. The substituted cyclopentenone moiety in **9** is a conspicuous structural feature that can be unraveled through cleavage of the $\Delta^{5,10}$ double bond to give diketone **10**. In the synthetic direction, exposure of **10** to a sufficiently basic medium could, under equilibrating conditions, result in deprotonation at C-5 to give an enolate. In the context of intermediate **10** such an enolate would be confined to a region of space proximal to an electrophilic carbonyl at C-10. In such a favorable setting, an intramolecular aldol condensation would be expected to be facile. The subsequent dehydration step to complete the assembly of **9** does not require special comment.

Retrosynthetic cleavage of the *trans* $\Delta^{8,9}$ disubstituted double bond in intermediate **11**, the projected precursor of diketone **10**, provides phosphorus ylide **12** and aldehyde **13** as potential precursors. In the forward sense, a Wittig reaction could conceivably achieve a convergent coupling of intermediates **12** and **13** with concomitant formation of the requisite *trans* C8–C9 olefin. Ordinarily, the union of a nonstabilized ylide, such as **12**, with an aldehyde would be expected to afford an alkene with a *cis* geometry.⁸ Fortunately, however, the Schlosser modification of the Wittig reaction permits the construction of *trans* olefins from aldehydes and nonstabilized phosphorus ylides.⁹

It would be expected that a few straightforward steps could accomplish the transformation of alkyl bromide **14** into phosphorus ylide **12** (Scheme 2b). On the other hand, the evolution of **14** from substituted aromatic furan ring **15** may not be obvious. It is, in fact, conceivable that the action of ethylene glycol on substituted furan **15** could, in the presence of an acid catalyst, result in the formation of **14**. The versatile furan nucleus can be regarded as a stable surrogate for a 1,4-dicarbonyl. Retrosynthetic cleavage of the indicated bond in **15** provides 2-methylfuran (**16**) and 1,4-dibromobutane (**17**) as potential precursors. In the synthetic direction, exposure of **16** to a strong base would be expected to result in deprotonation at C-5 to give a reactive carbon nucleophile which could subsequently be alkylated by **17**.¹⁰

A salient structural feature of intermediate **18** (Scheme 2b), the retrosynthetic precursor of aldehyde **13**, is its γ,δ -unsaturated ester moiety. As it turns out, the Johnson ortho ester variant of the Claisen rearrangement is an excellent method for the synthesis of γ,δ -unsaturated esters.¹¹ In fact, the Claisen rearrangement, its many variants included, is particularly valuable in organic synthesis as a method for the stereocontrolled construction of *trans* di- and tri-substituted carbon–carbon double bonds.^{12,13} Thus, it is conceivable that intermediate **18** could be fashioned in one step from allylic alcohol **20** through a Johnson ortho ester Claisen rearrangement. In

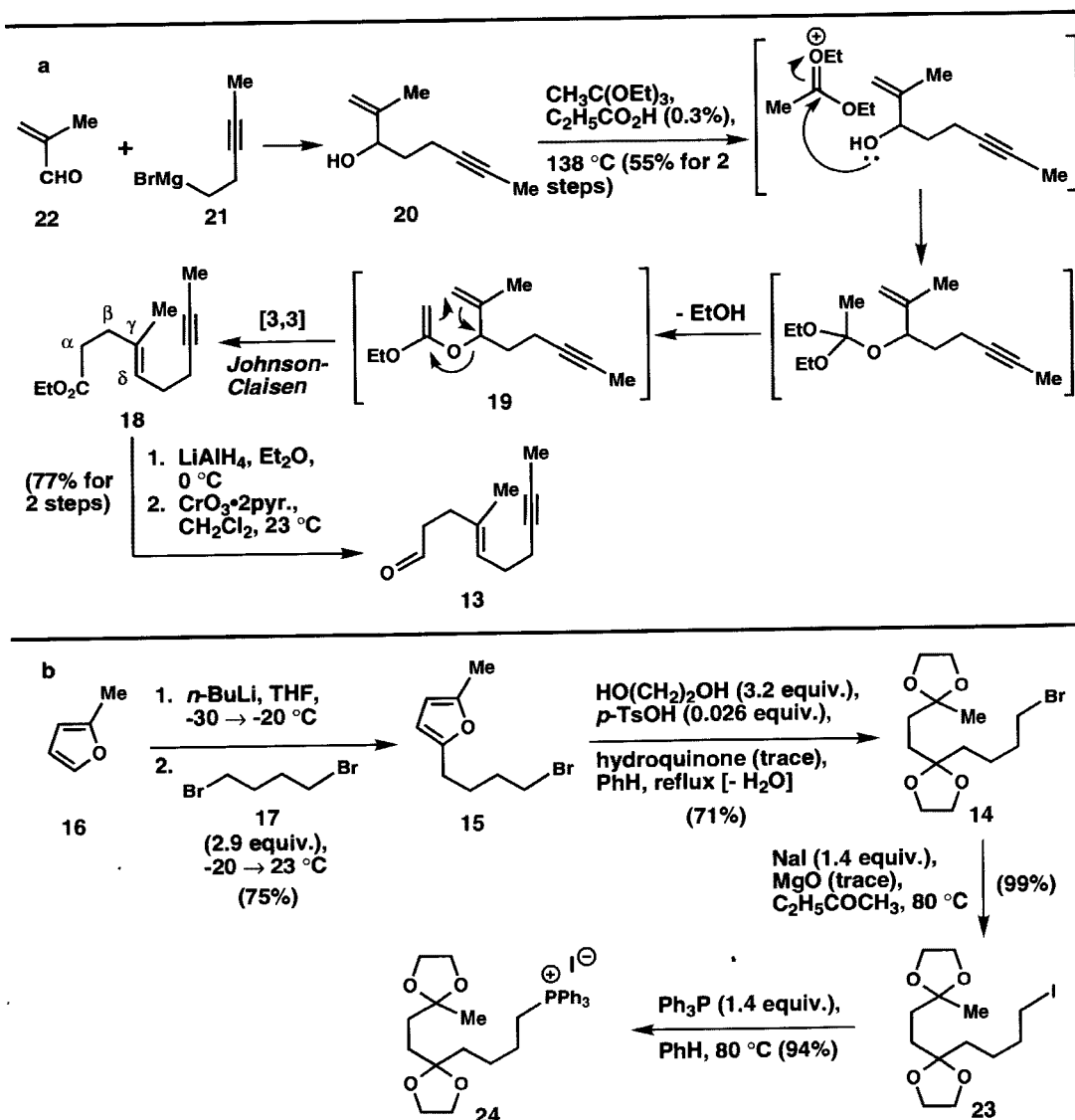


Scheme 2b. Retrosynthetic analysis of progesterone (**1**) (continued).

the synthetic direction, treatment of **20** with triethyl orthoacetate in the presence of a catalytic quantity of propionic acid could lead, through the intermediacy of mixed-ketene acetal **19**, to the formation of γ,δ -unsaturated ethyl ester **18**. Alcohol **20** could be derived in one step through alkylation of methacrolein (**22**) with Grignard reagent **21**.

6.3 Total Synthesis

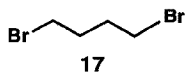
Johnson's classic synthesis of progesterone (**1**) commences with the reaction of 2-methacrolein (**22**) with the Grignard reagent derived from 1-bromo-3-pentyne to give allylic alcohol **20** (see Scheme 3a). It is inconsequential that **20** is produced in racemic form because treatment of **20** with triethyl orthoacetate and a catalytic amount of propionic acid at 138 °C furnishes **18** in an overall yield of 55 % through a process that sacrifices the stereogenic center created in the carbonyl addition reaction. In the presence of propionic acid, allylic alcohol **20** and triethyl orthoacetate combine to give



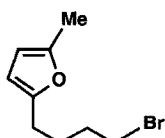
Scheme 3. Synthesis of intermediates 13 (a) and 24 (b).



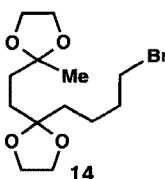
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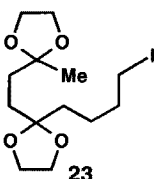
17



15



14



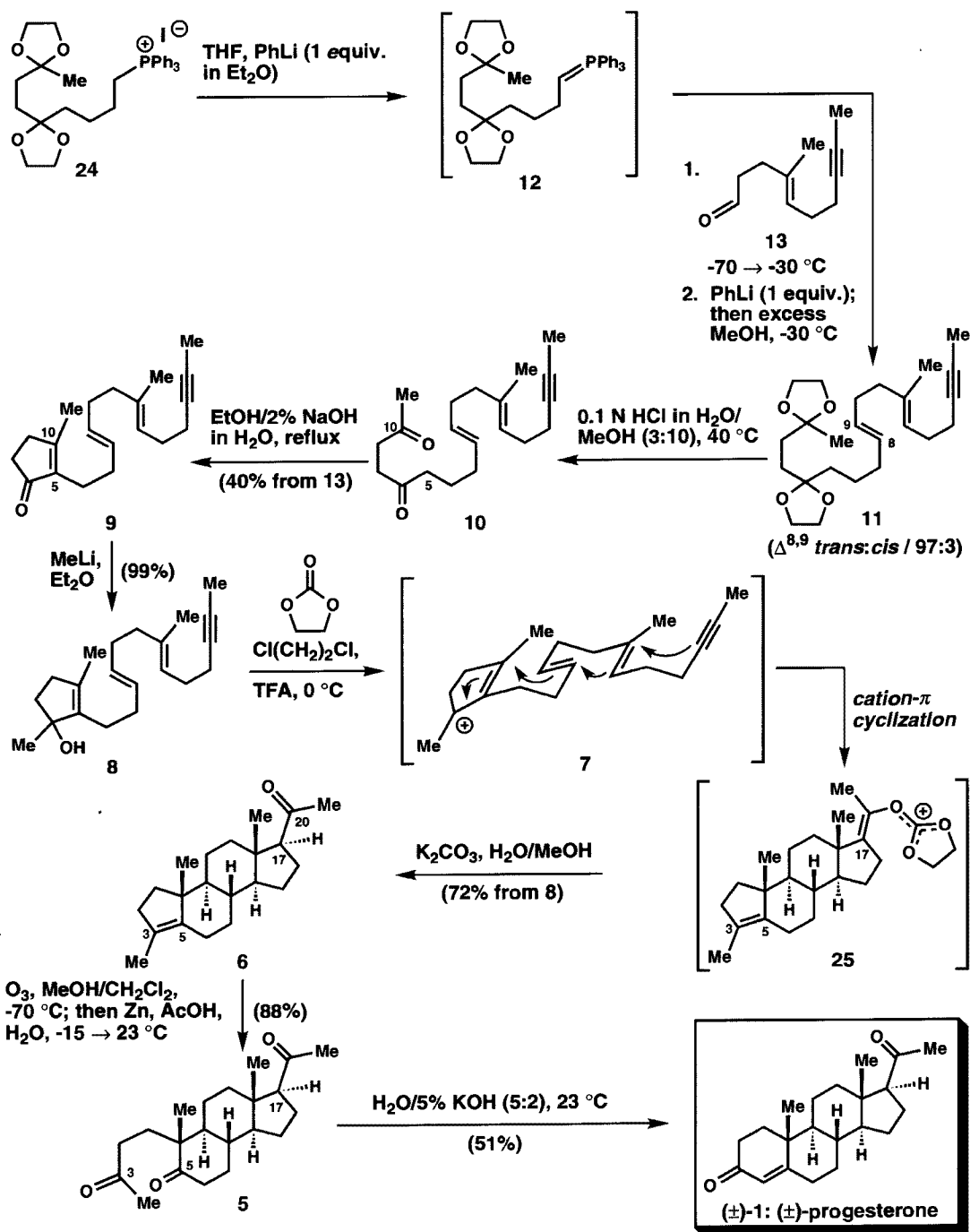
23

mixed-ketene acetal **19**, an intermediate which participates in a Claisen rearrangement to give γ,δ -unsaturated ester **18**. Reduction of the ethyl ester in **18** with lithium aluminum hydride furnishes a primary alcohol which, in crude form, is oxidized with Collins reagent to aldehyde **13** in a yield of 77 % from **18**.

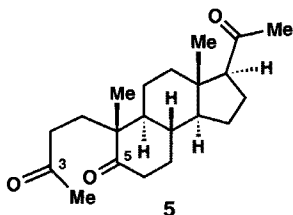
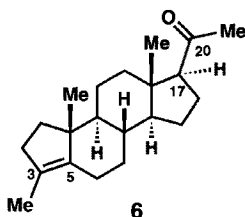
The synthesis of phosphonium iodide **24**, the precursor of phosphorus ylide **12**, begins with the alkylation of 5-lithio-2-methylfuran,¹⁰ derived from the action of *n*-butyllithium on 2-methylfuran (**16**), with 1,4-dibromobutane (**17**) to give **15** in 75 % yield (see Scheme 3b). It is instructive at this point to reiterate that the furan nucleus can be used in synthesis as a progenitor for a 1,4-dicarbonyl. Whereas the action of aqueous acid on a furan is known to provide direct access to a 1,4-dicarbonyl compound, exposure of a furan to an alcohol and an acid catalyst should result in the formation of a 1,4-diketal. Indeed, when a solution of intermediate **15** in benzene is treated with excess ethylene glycol, a catalytic amount of *para*-toluenesulfonic acid, and a trace of hydroquinone at reflux, bisethylene ketal **14** is formed in a yield of 71 %. The azeotropic removal of water provides a driving force for the ketalization reaction, and the presence of a trace of hydroquinone suppresses the formation of polymeric material. Through a Finkelstein reaction,¹⁴ the action of sodium iodide on primary bromide **14** results in the formation of primary iodide **23**, a substance which is then treated, in crude form, with triphenylphosphine to give crystalline phosphonium iodide **24** in a yield of 93 % from **14**.

We are now in a position to address the union of intermediates **24** and **13** (see Scheme 4). Although we will not discuss issues relevant to the mechanism of the Wittig reaction here,^{8d,15} it is important to recall that it is possible to achieve the formation of *trans* alkenes through Wittig reactions between aldehydes and non-stabilized phosphorus ylides.⁹ Thus, according to Schlosser's procedure, treatment of phosphonium iodide **24** with one equivalent of phenyllithium furnishes phosphorus ylide **12** which is immediately treated, at -70°C , with aldehyde **13**. After warming of the solution to -30°C , a second equivalent of phenyllithium is added, followed by excess methanol. The convergent union of intermediates **12** and **13**, in this manner, results in the formation of a 97:3 mixture of C8-C9 olefin stereoisomers in favor of the desired *trans* olefin **11**. Exposure of this mixture to 0.1 *N* aqueous HCl in methanol at 40°C accomplishes the hydrolysis of both ketal protecting groups and provides diketone **10**. Treatment of crude diketone **10** with aqueous sodium hydroxide in ethanol at reflux induces aldol cyclodehydration and affords, after purification, enone **9** in a yield of 40 % from **13**.

The stage is now set for the crucial polycyclization event. Tertiary carbinol **8**, derived from the action of methyllithium on enone **9**, is a rather unstable substance, and it was submitted to the polycyclization reaction without purification. When intermediate **8** is treated with trifluoroacetic acid (TFA) and the vinyl cation trapping agent ethylene carbonate in 1,2-dichloroethane at 0°C , the desired



Scheme 4. Synthesis of (±)-progesterone [(±)-1].



tricyclization reaction takes place with impressive facility and provides a 5:1 mixture of 17β (intermediate **6**) and 17α diastereomers after workup with aqueous potassium carbonate in methanol. It is presumed that exposure of **8** to TFA induces a heterolytic cleavage of the C–O bond to give tertiary allylic cation **7** which subsequently participates in a cation– π tricyclization reaction. Interception of the resultant linear vinyl cation with ethylene carbonate affords **25** which undergoes facile conversion to methyl ketone **6** during workup.

The final two stages are very straightforward. Oxidative scission of the C3–C5 double bond in **6** with ozone provides triketone **5** which, without purification, is subjected to a base-induced intramolecular aldol/dehydration reaction. The crystalline product obtained from this two-step sequence (45 % overall yield) was actually an 85:15 mixture of (\pm)-progesterone and a diastereomeric substance, epimeric at C-17. Two recrystallizations afforded racemic progesterone [(\pm)-(**1**)] in diastereomerically pure form.

6.4 Conclusion

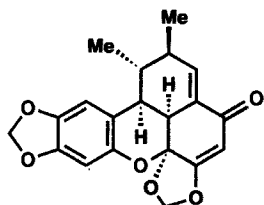
Ever since the elucidation of the elaborate yet simple pathway by which the cholesterol molecule is assembled in nature, organic chemists have been captivated by the impressive productivity of polyolefinic cyclizations. The emergence of biomimetic polyolefinic cyclizations as viable synthetic strategies is due to the pioneering efforts of the groups of W.S. Johnson^{2a–c,16} and E.E. Van Tamelen.^{2d–i} The extensive and brilliant contributions of these two groups have enriched the total synthesis field and have provided the foundation for some elegant recent achievements.¹⁷

The development of novel strategies for initiating and terminating the polyolefin cascade is a particularly noteworthy contribution by Johnson *et al.* that has expanded the scope of polyolefinic cyclizations. In this synthesis, we witnessed the facility with which the polyolefin cascade can be executed using the tertiary allylic alcohol function as an initiator. As shown by Johnson *et al.*, acetals are also very capable initiators of polyolefinic cyclizations in the presence of Lewis acids. With regard to the termination event, the methylacetylenic function is an effective cyclization terminator that permits the formation of a *trans*-fused five-membered ring,¹⁸ and that performs admirably in the synthesis of 20-keto steroids.^{6b} In more recent studies, Johnson *et al.* have demonstrated the viability of propargylic silanes,¹⁹ allylic silanes,²⁰ and vinyl fluorides²¹ as terminating groups for biomimetic polyene cyclizations. In addition, during the course of studies aimed at the development of a unified strategy for the synthesis of the hypocholesterolemic mevinic acids (e.g. Mevacor®), S.D. Burke and his group at Wisconsin have also demonstrated that vinylsilanes are very effective terminators of cationic polyene cyclizations.^{17,22}

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1: carpanone

O. L. Chapman (1971)

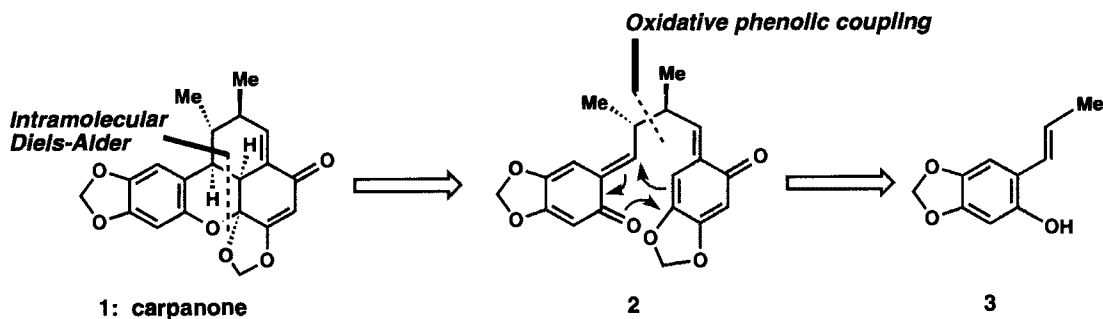
Carpanone

7.1 Introduction

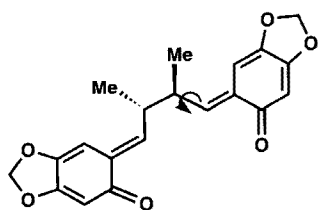
The structure of carpanone (**1**) was revealed by Australian scientists in 1969.¹ Carpanone, a hexacyclic molecule and host of five contiguous stereogenic centers, is a lignan found in the bark of the carpano tree.

7.2 Retrosynthetic Analysis and Strategy

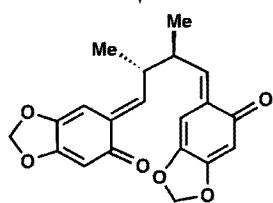
Although carpanone's complex structure possesses no element of symmetry, it was suggested¹ that carpanone could form in nature through an intramolecular cycloaddition of a C_2 -symmetric bis(qui-



Scheme 1. Presumed biosynthesis and retrosynthetic analysis of carpanone (**1**).

2 (C_2 -symmetric)

C-C bond
rotation



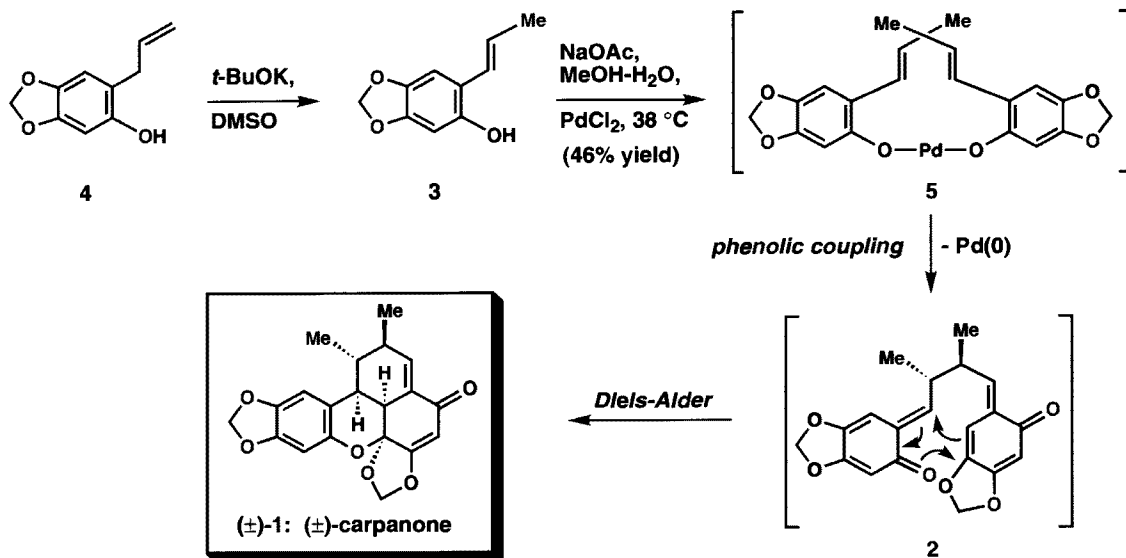
2

nodimethide) (see **2**, Scheme 1). An internal cycloaddition of this type would be particularly productive, for it would simultaneously create two rings and three contiguous stereocenters. C_2 -symmetric bis(quinodimethide) **2** could conceivably be produced by an oxidative dimerization ($\beta\beta$ -phenolic coupling) of intermediate **3**. Based on this intriguing biosynthetic proposal, Chapman *et al.* disclosed, in 1971, a remarkable two-step synthesis of the lignan carpanone.²

7.3 Total Synthesis

The elegant biomimetic synthesis of carpanone by Chapman and coworkers commences with the base-induced isomerization of 2-allyl-4,5-methylenedioxyphenol (**4**)³ to 2-(*trans*-1-propenyl)-4,5-methylenedioxyphenol (**3**) (see Scheme 2). Compound **3**, as simple as it is, is actually the key intermediate in this synthesis; oxidative dimerization of **3** could result in the formation of carpanone (**1**) through the intermediacy of the C_2 -symmetric and highly reactive bis(quinodimethide) **2**.

Palladium dichloride (PdCl_2) was carefully chosen to effect the desired oxidative coupling reaction. Although phenolic couplings have traditionally been achieved with one-electron oxidants, it was anticipated that PdCl_2 , containing as it does a divalent metal, could facilitate the crucial oxidative coupling step by bringing two phenolic units together (see intermediate **5**). By rendering the phenolic



Scheme 2. Synthesis of (±)-carpanone [(±)-1].

coupling reaction intramolecular, it might also be possible to control the stereochemical course of the carbon–carbon bond forming event (see **5** → **2**).

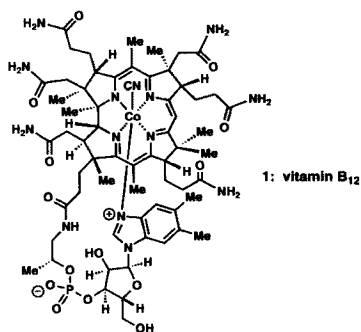
In the event, treatment of a rapidly stirred solution of **3** and sodium acetate in MeOH–H₂O at 38 °C with PdCl₂ results in the formation of carpanone (**1**) in 46 % yield. The ordered unimolecular transition state for the oxidative coupling reaction furnishes putative bis(quinodimethide) **2** stereoselectively. Once formed, **2** readily participates in an intramolecular Diels–Alder reaction⁴ to give carpanone (**1**). Two new rings and all five contiguous stereocenters are created in this spectacular sequential transformation.⁵

7.4 Conclusion

Organic syntheses based on biosynthetic proposals are often extremely concise and elegant.⁶ Although the constitution and stereochemical complexity of carpanone may seem formidable, the sequential application of the Diels–Alder and oxidative phenolic coupling transforms⁷ to the natural product provides an exceedingly efficient solution. Chapman's striking synthesis of carpanone typifies the power of biomimetic synthetic strategies.

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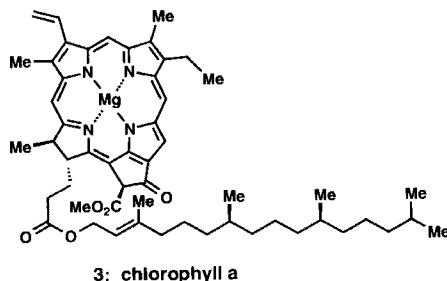
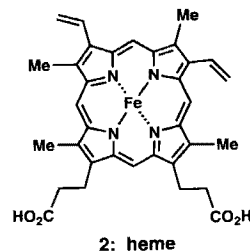
R. B. Woodward and A. Eschenmoser (1973)

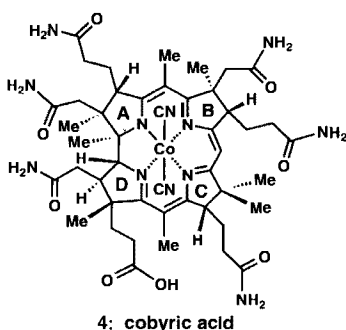
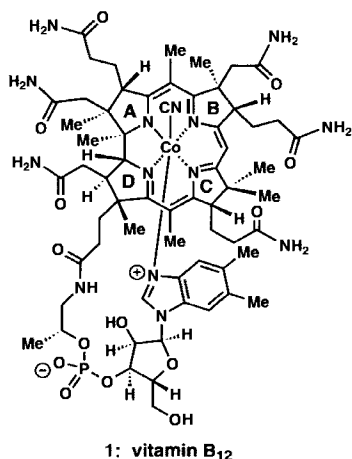
Vitamin B₁₂

8.1 Introduction

The total synthesis of vitamin B₁₂, the result of a close collaboration between the late Professor R. B. Woodward and his group at Harvard and Professor Albert Eschenmoser and his group at ETH Zürich, stands as one of the greatest achievements of synthetic organic chemistry.^{1a-d} Few natural product syntheses can match the pervasive impact that the total synthesis of vitamin B₁₂ has had on the science of organic chemistry. Novel bond-forming strategies, ingenious solutions to formidable synthetic problems, elegant applications of organic synthesis methodology, intriguing hypotheses about the biogenesis of vitamin B₁₂,² and the principles of orbital symmetry conservation³ all issued from this landmark achievement.

The vitamin B₁₂ story began in 1956 with the impressive X-ray crystallographic studies of Dorothy Crowfoot-Hodgkin and her collaborators which culminated in the elucidation of the complete structure of vitamin B₁₂ (**1**).⁴ By virtue of the stereochemical and constitutional complexity of the structure of vitamin B₁₂, these studies constituted, at the time, a great achievement in X-ray crystallography, and they provided a firm footing for serious synthetic studies. There is an interesting homology between the structures of vitamin B₁₂ (**1**), the blood pigment heme (**2**), and the leaf pigment chlorophyll a (**3**). Each molecule possesses a macrocyclic nucleus comprising four five-membered heterocyclic rings A, B, C, and D, and organized around a central metal atom. As we shall see later, the binding of a metal atom by the corrin nucleus of vitamin B₁₂ is a very useful property shared by precorrinoid structures (i.e. uncyclized corrin precursors). The binding of a metal atom by linear precorrinoid intermediates pre-organizes their structure and facilitates cyclization reactions.



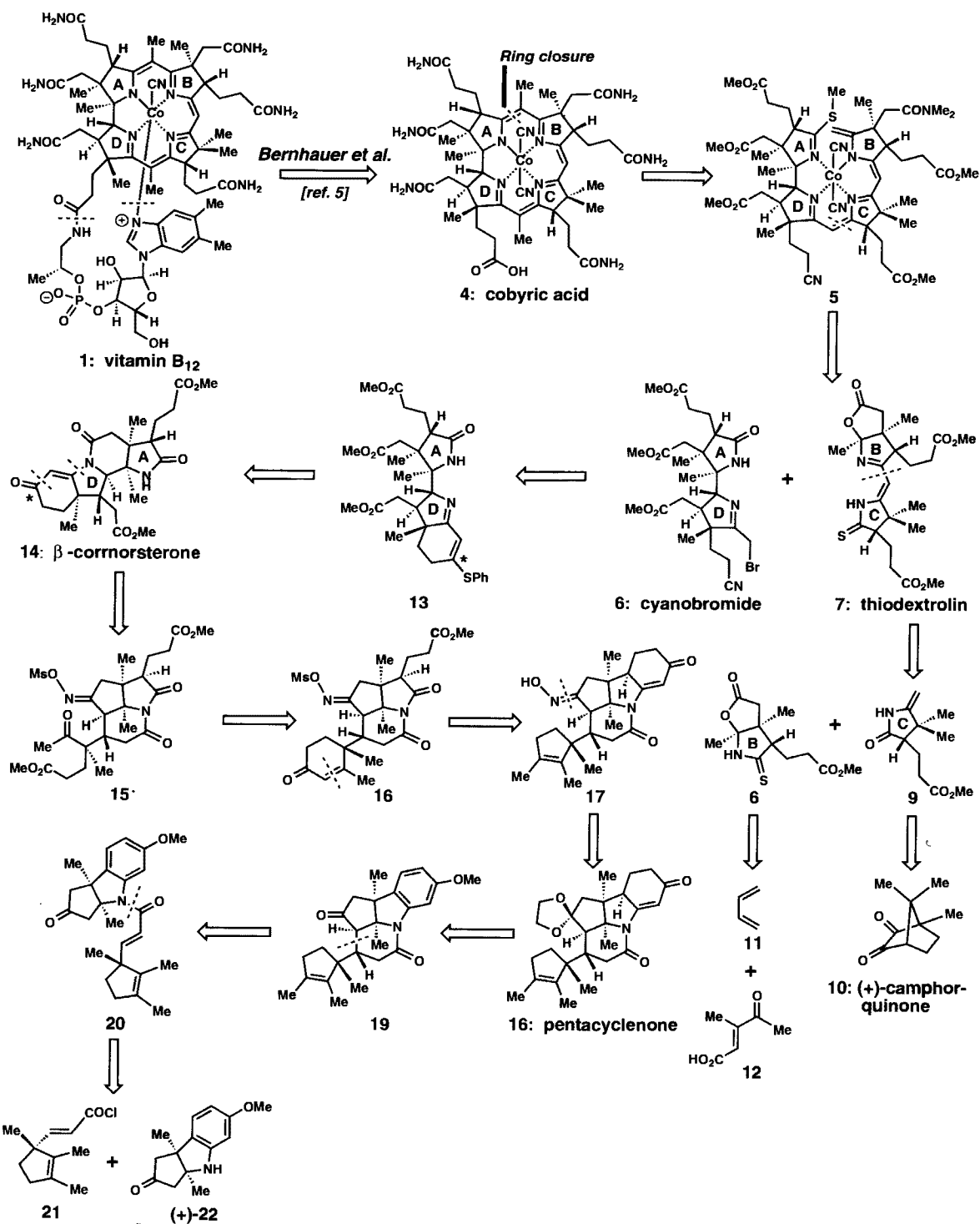


Although there are gross structural similarities between these three molecules, there is an important difference. Unlike the more modestly functionalized relatives heme and chlorophyll a, vitamin B₁₂ is rich in stereochemical detail. Organized around the periphery of the nucleus of vitamin B₁₂ (**1**) are nine asymmetric carbon atoms. Six of these are contiguous and are concentrated in the left wing, or A–D sector, of the molecule, while the remaining three are distributed between rings B and C. The spatial relationships among the various sectors of vitamin B₁₂ are such that it would be very difficult to use preexisting stereocenters in one sector to direct the stereochemical course of reactions that create new stereocenters in any of the other sectors. This situation mandates the adoption of a synthetic strategy wherein each sector or building block is prepared in enantiomerically pure form first and then joined with neighboring sectors. This convergent approach to the synthesis of vitamin B₁₂ could be highly efficient, and it could secure correct relative stereochemical relationships. Another point of interest is the observation that six out of seven side chains attached to the periphery of the vitamin B₁₂ nucleus terminate in a simple amide group, while the seventh accommodates a sequence of isopropanolamine, phosphate, ribose, and dimethylbenzimidazole groups. The last of these groups is also coordinated to the central cobalt atom.

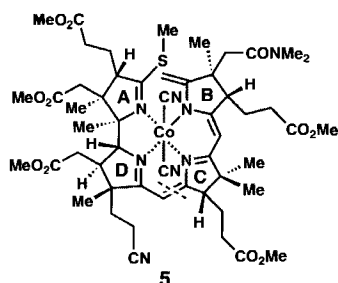
When the Woodward–Eschenmoser synthesis began, it was known from the work of Bernhauer *et al.*⁵ that cobyric acid (**4**), a naturally occurring substance, could be converted directly into vitamin B₁₂. Thus, the synthetic problem was reduced to the preparation of cobyric acid, a molecule whose seventh side chain terminates in a carboxylic acid group and is different from the other side chains. Two strategically distinct and elegant syntheses of the cobyric acid molecule evolved from the combined efforts of the Woodward and Eschenmoser groups and both will be presented. Although there is naturally some overlap, the two variants differ principally in the way in which the corrin nucleus is assembled.

8.2 Retrosynthetic Analysis and Strategy

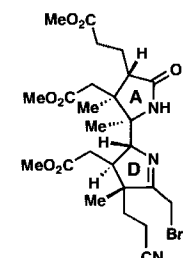
Scheme 1 outlines the retrosynthetic analysis of the Woodward–Eschenmoser A–B variant of the vitamin B₁₂ (**1**) synthesis. The analysis begins with cobyric acid (**4**) because it was demonstrated in 1960 that this compound can be smoothly converted to vitamin B₁₂.⁵ In two exploratory corrin model syntheses to both approaches to the synthesis of cobyric acid,⁶ the ability of secocorrinoid structures (e.g. **5**) to bind metal atoms was found to be central to the success of the macrocyclization reaction to give intact corrinoid structures. In the Woodward–Eschenmoser synthesis of cobyric acid, the cobalt atom situated in the center of intermediate **5** organizes the structure of the secocorrin, and promotes the cyclization



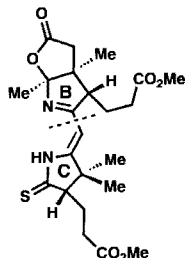
Scheme 1. Retrosynthetic analysis of the Woodward–Eschenmoser synthesis of cobyrinic acid (**4**).



reaction by bringing into spatial proximity the reactive functional groups contained within rings A and B of intermediate **5**. Retrosynthetic disconnection of **5** is most productive, for it furnishes two fragments of comparable complexity representing the left and right wings of the molecule. Fragment **6**, the left wing or A–D sector, is referred to as cyanobromide, and it contains the six contiguous asymmetric carbon atoms. This intermediate was the conquest of Woodward's group at Harvard. The bromine atom in this intermediate is to serve as a leaving group in a reaction that will allow the two halves of the molecule to be joined. In addition, it is interesting to note that the side chain that is destined to terminate in a carboxylic acid group is differentiated from the others. It is historically significant that important observations were made during the course of the synthesis of compound **6** that provided the impetus for the development of the Woodward–Hoffmann rules for orbital symmetry conservation.³

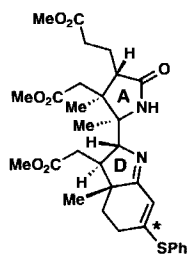


6: cyanobromide

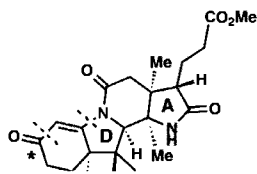


7: thiodextrolin

Thiodextrolin (**7**), an intermediate that was prepared by the Eschenmoser group at ETH, represents the right-wing portion of cobyrinic acid, and it contains rings B and C. An interesting structural feature of thiodextrolin is the thioamide grouping; this conspicuous function imparts nucleophilic character to intermediate **7**. In the synthetic direction (*vide infra*), the electrophilic cyanobromide **6** and the nucleophilic thiodextrolin (**7**) are joined by an alkylative Eschenmoser sulfide contraction reaction.⁷ Retrosynthetic simplification of thiodextrolin (**7**) is rather straightforward furnishing rings B (**8**) and C (**9**). In contrast to the nucleophilic thioamide in thiodextrolin, the thioamide present in B-ring intermediate **8** is to be used as an electrophile in an interesting oxidative Eschenmoser coupling reaction⁷ with the nucleophilic enamide present in C-ring intermediate **9**. A clever sequence of reactions commencing with a Diels–Alder reaction⁸ between butadiene (**11**) and β -methyl- β -acetylacrylic acid (**12**) could potentially furnish intermediate **8**, and a concise sequence starting from (+)-camphorquinone (**10**) could give intermediate **9**.



13

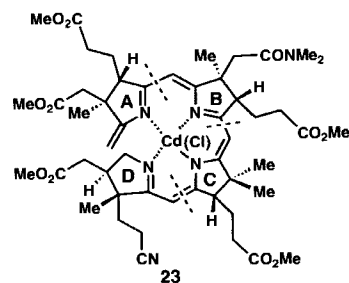
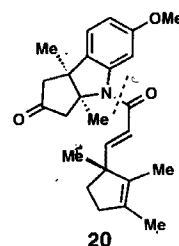
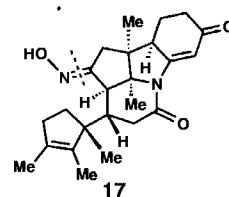
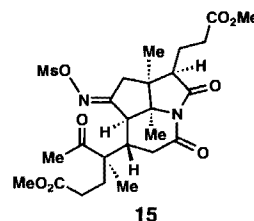
14: β -cornnorsterone

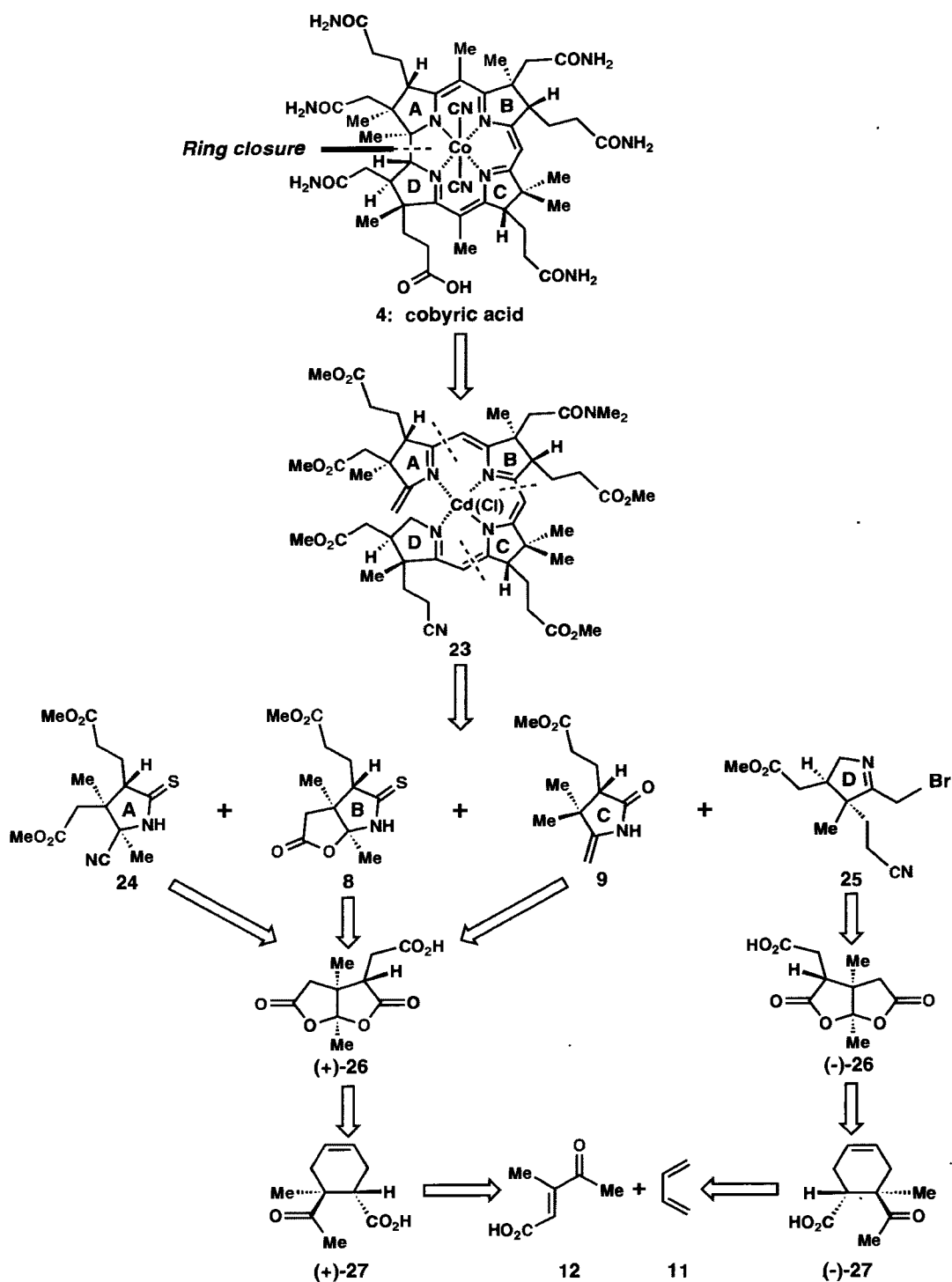
A retrosynthetic analysis of cyanobromide **6** is much less straightforward. The structural relationship between cyanobromide **6** and its predecessor, intermediate **13**, is close. An oxidative scission of the thioether double bond in **13** would furnish an *S*-phenyl thioate at one terminus and an aldehyde at the other. A straightforward sequence of functional group interconversions could then complete the synthesis of cyanobromide **6**. β -Cornnorsterone (**14**), a key intermediate which derives its name from its structural relationship to corrins and steroids, carries the six contiguous stereogenic centers present in the corresponding part of vitamin B₁₂. Although the homology between intermediate **13** and β -cornnorsterone may seem vague, compound **13** could conceivably be formed in one step from **14**. In the event that methanol and thio-phenol could be induced to react with **14** in a completely chemoselective fashion, then **13** would form after loss of a water molecule. By far the most productive single-step transformation in the synthe-

sis of cyanobromide **6** is the conversion of oxime mesylate **15** into a stereoisomeric mixture of α - and β -cornorsterones. These two diastereomeric substances are epimeric at the stereocenter adjacent to the ring A lactam carbonyl and, for clarity, only the desired isomer **14** is indicated. In this amazing transformation, the five-membered ring that bears the oxime mesylate is converted into a six-membered lactam ring through a Beckmann rearrangement.⁹ It is important to note that the stereochemistry of the oxime mesylate in **15** would ensure that the carbon–carbon bond *trans* to the mesylate will migrate during the Beckmann rearrangement. Once the six-membered lactam ring is formed, its nitrogen atom would find itself in proximity to the ketone carbonyl group. This nitrogen atom could then attack the ketone carbonyl group, and, at some point, the active methyl group of the ketone could attack the methoxycarbonyl group. Three new rings could potentially be formed in this very productive transformation. Ozonolytic scission of both carbon–carbon double bonds in intermediate **17**, followed sequentially by esterification, intramolecular cyclodehydration, and mesylation reactions could conceivably furnish intermediate **16**. Cleavage of the carbon–carbon double bond in **16**, again with ozone, followed by treatment with diazomethane, was projected to give intermediate **15**.

A sequence of straightforward functional group interconversions leads from **17** back to compound **20** via **18** and **19**. In the synthetic direction, a base-induced intramolecular Michael addition reaction could create a new six-membered ring and two stereogenic centers. The transformation of intermediate **20** to **19** would likely be stereoselective; substrate structural features inherent in **20** should control the stereochemical course of the intramolecular Michael addition reaction. Retrosynthetic disassembly of **20** by cleavage of the indicated bond provides precursors **21** and **22**. In the forward sense, acylation of the nitrogen atom in **22** with the acid chloride **21** could afford amide **20**.

Scheme 2 outlines the retrosynthetic analysis of the Eschenmoser variant of the synthesis of cobyrinic acid (**4**). The approach outlined in Scheme 1 represents the A–B variant; it accomplishes the assembly of the macrocyclic corrin nucleus of cobyrinic acid by a cyclization reaction that creates a carbon–carbon bond between rings A and B. An unconventional and equally elegant approach, the A–D variant, was developed in Zürich by the Eschenmoser group. The distinguishing feature of the A–D variant is the ring closure joining rings A and D via a metal template assisted, photo-induced cycloisomerization of secocorrin metal complex **23**.^{1d} It is noteworthy that this reaction is quite facile and it creates the natural configuration at the A–D junction with 95% stereoselectivity. Since the Eschenmoser strategy solves both the *trans* A–D junction and the macrocyclization problems in one impressive step, the synthetic problem is reduced to the synthesis of the four heterocyclic rings A (**24**), B (**8**), C (**9**), and D (**25**), each one in enantiomerically pure form, and the development of





Scheme 2. Retrosynthetic analysis of the Eschenmoser synthesis of cobyrinic acid (**4**).

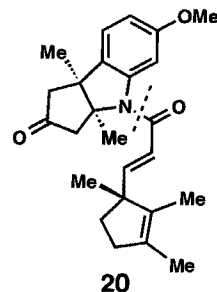
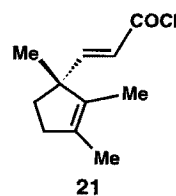
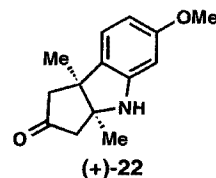
efficient coupling strategies. An elegant feature of the A–D variant is the recognition that all four heterocyclic rings could be elaborated from a single racemic precursor! Rings A (**24**), B (**8**), and C (**9**) could potentially be synthesized from dextrorotatory dilactone (+)-**26**, while ring D (**25**) could be obtained from levorotatory dilactone (–)-**26**. Compound **27**, the projected product of a Diels–Alder reaction between butadiene (**11**) and β -methyl- β -acetylacrylic acid (**12**), is to be prepared in racemic form. The enantiomers of **27** could then be obtained, in pure form, through a classical resolution. Incidentally, the absolute configuration of (+)-**27** was established by the Eschenmoser group through correlation of a derivative with a degradation fragment obtained from vitamin B₁₂.^{1a} Independent treatment of both antipodes of **27** with chromic acid could then furnish both enantiomers of dilactone **26**. As we will see later in the synthesis, both groups adopted the same strategy for the synthesis of the B-ring of cobyrinic acid (**4**).

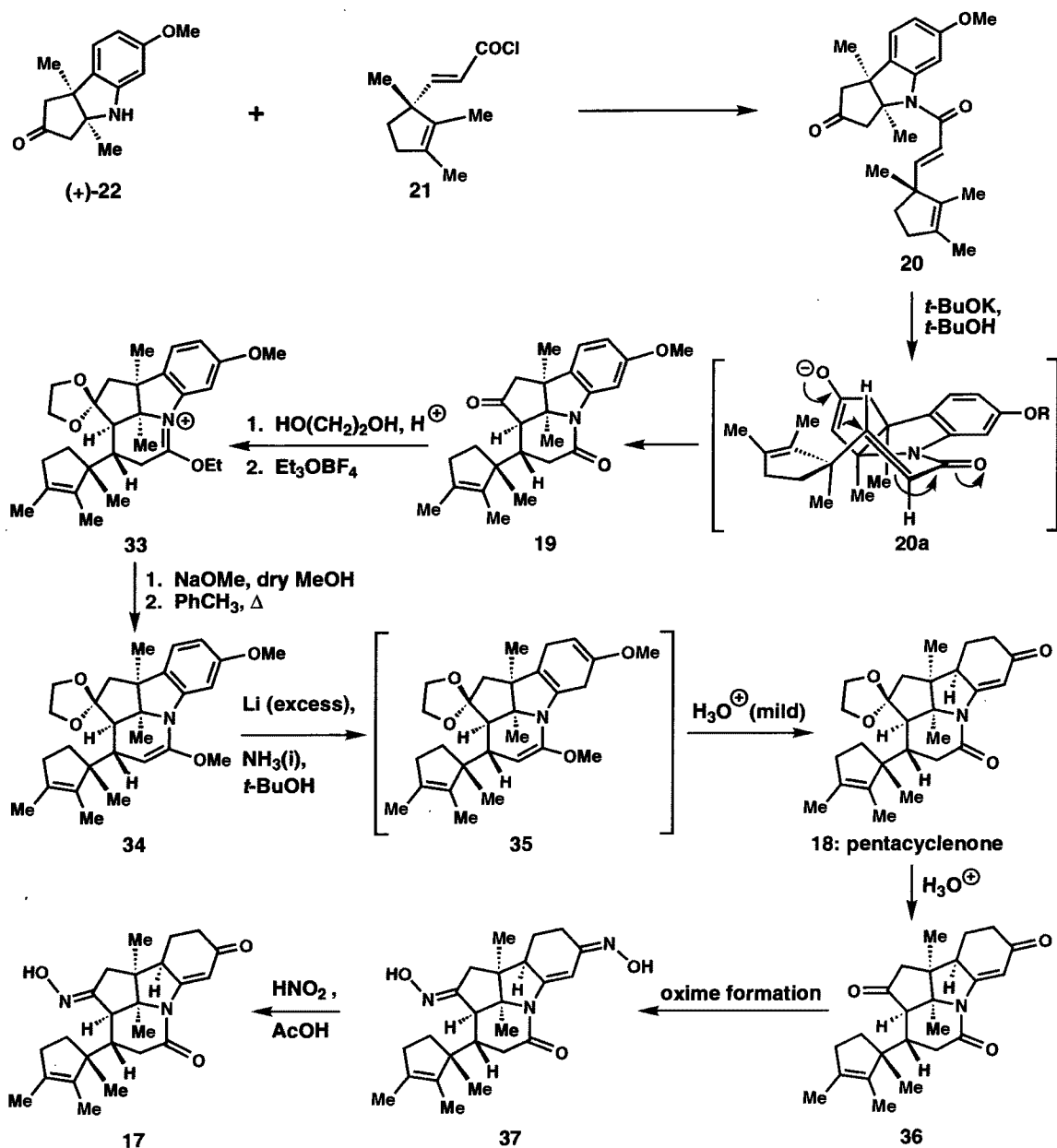
8.3 Total Synthesis

8.3.1 The Woodward Synthesis of Cyanobromide **6**

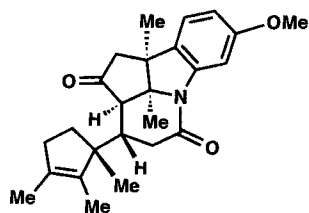
Schemes 3–7 describe the synthesis of cyanobromide **6**, the A–D sector of vitamin B₁₂. The synthesis commences with an alkylation of the magnesium salt of methoxydimethylindole **28** to give intermediate **29** (see Scheme 3a). The stereocenter created in this step plays a central role in directing the stereochemical course of the next reaction. Thus, exposure of **29** to methanol in the presence of BF₃ and HgO results in the formation of tricyclic ketone **22** presumably through the intermediacy of the derived methyl enol ether **30**. It is instructive to point out that the five-membered nitrogen-containing ring in **22**, with its two adjacent methyl-bearing stereocenters, is destined to become ring A of vitamin B₁₂. A classical resolution of racemic **22** with α -phenylethylisocyanate (**31**) furnishes tricyclic ketone **22** in enantiomerically pure form via diastereomer **32**.

Intermediate **22** possesses several nucleophilic sites. Acylation of the nitrogen atom in **22** with acid chloride **21**, a substance that can be prepared in enantiomerically pure form from (–)-camphor according to Scheme 3b, furnishes ketone amide **20**, and sets the stage for an intramolecular Michael addition reaction (Scheme 4). Treatment of **20** with potassium *tert*-butoxide affords a ketone enolate which reacts intramolecularly with the α,β -unsaturated amide to give intermediate **19** as a single diastereomer. The diastereoselection exhibited in this reaction is thought to be a consequence of the concave nature of intermediate **20a**, and the minimization of nonbonding interactions in the transition state for the carbon–carbon bond forming reaction.

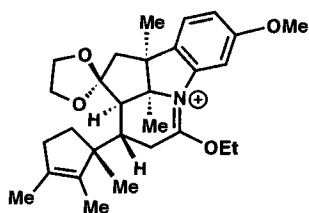




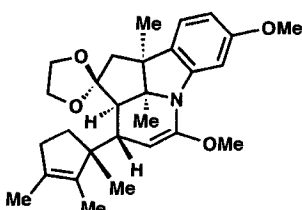
Scheme 4. The Woodward synthesis of intermediate 17.



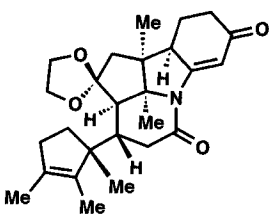
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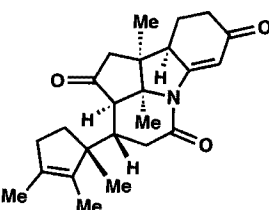
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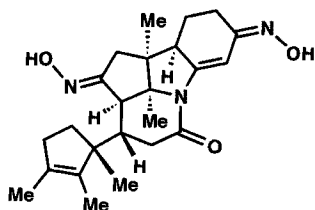
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18: pentacyclenone



36



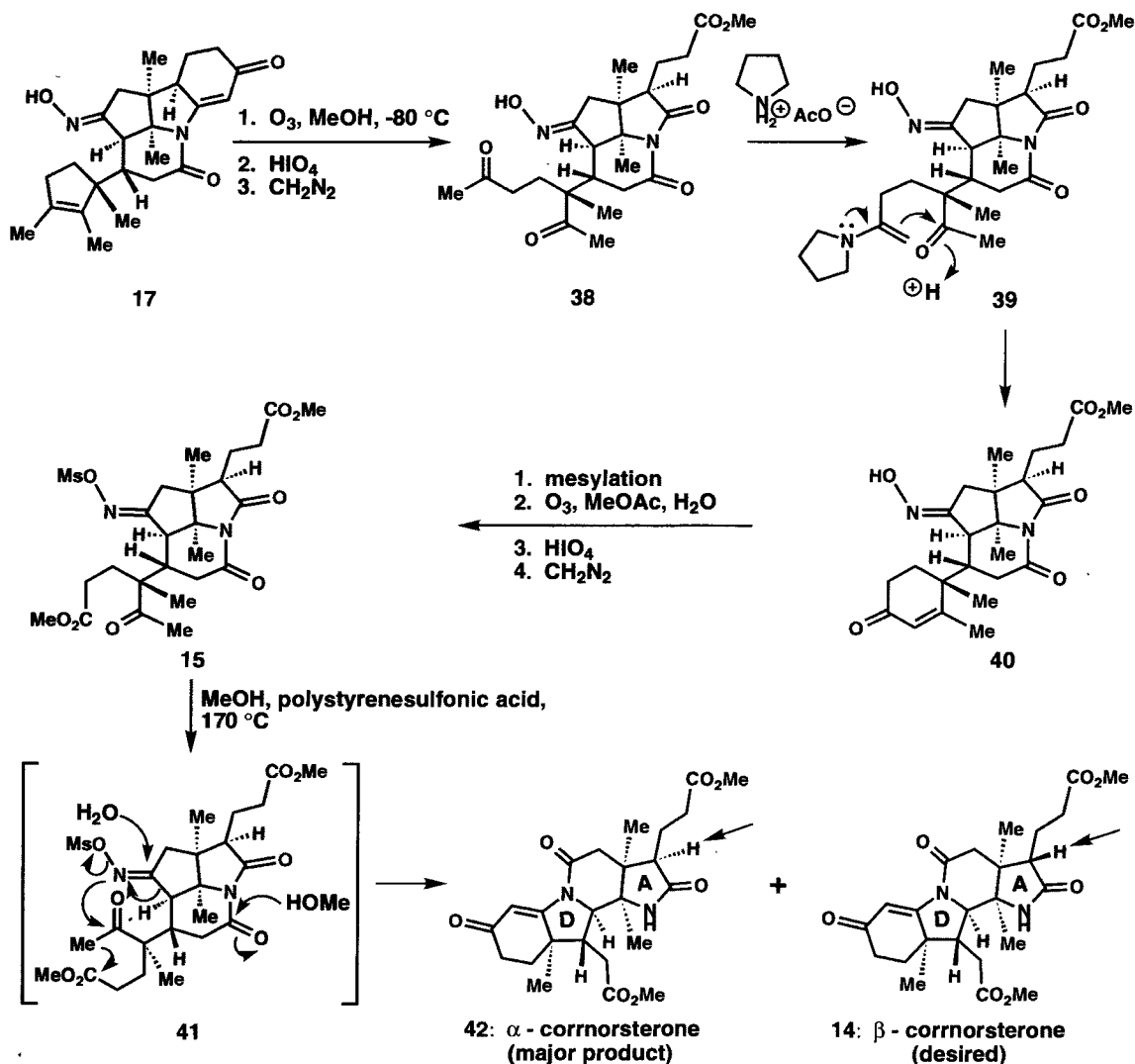
37

When stable substitutes for sensitive functional groups are used in a synthesis, it is certainly advantageous to modify them in a useful way rather than destroy them. Up to this point, the electron-rich aromatic ring has served as a stable surrogate for a carbonyl group and a propionate ester side chain. In order to make use of the carbon atoms that constitute the stable aromatic ring, it is obvious that a reduction⁹ needs to be performed. A dissolving-metal or Birch reduction⁹ can accomplish this task, but intermediate **19** is not a suitable substrate for such a reduction because it possesses other easily reducible functional groups. After a conventional ketalization of the ketone in **19**, the oxygen atom of the amide carbonyl is alkylated selectively with Meerwein's salt (Et_3OBF_4) to give iminoester **33**. A simple two-step sequence of reactions then gives intermediate **34**, a suitably protected molecule which is now a viable substrate for a Birch reduction. In the event, the aromatic ring in **34** is reduced to the dihydro level (see **35**) with lithium metal in a solution of liquid ammonia and *tert*-butanol. Interestingly, the hydrolysis of two of the three acid-labile functional groups in **35** with mild aqueous acid is attended by migration of the tetrasubstituted C–C double bond into conjugation with the carbonyl (see intermediate **18**). Note also that a new stereogenic center is created in this step.

Pentacyclenone, the trivial name given to intermediate **18**, contains a single nitrogen atom which will eventually be expressed in the A-ring of vitamin B₁₂. The synthesis of the targeted A–D sector requires incorporation of one more nitrogen atom which is introduced, in the form of an oxime, through a straightforward three-step sequence of reactions. Not surprisingly, the action of aqueous acid on pentacyclenone (**18**) induces cleavage of the dioxolane ring and provides ketone **36**. At this stage in the synthesis, it was hoped that **36** could be converted directly into the desired monoxime **17**. Although oximation of **36** unavoidably leads to the formation of dioxime **37**, the unwanted oximino group can be readily and selectively cleaved with nitrous acid in acetic acid under mild conditions to give the desired monoxime **17**.

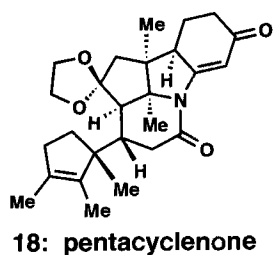
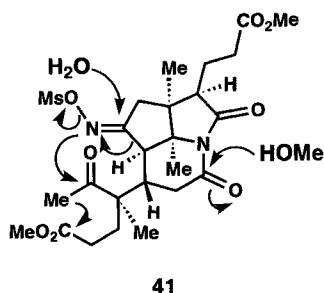
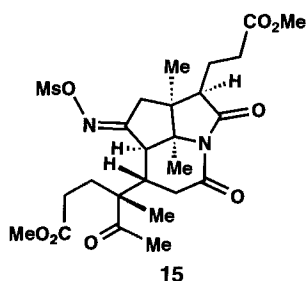
An important stereochemical issue requires comment at this time. It was anticipated that the oxime nitrogen in compound **17**, which is destined to become the D-ring nitrogen of vitamin B₁₂, could be introduced in proper relation to the A-ring nitrogen through a Beckmann rearrangement.⁹ As such is the case, the exclusive formation of the indicated oxime stereoisomer in the oximation reaction is significant because it ensures that migration of the desired carbon–carbon bond situated *trans* to the leaving group will occur during the Beckmann rearrangement.

Scheme 5 details the synthesis of β -cormnorsterone (**14**) from **17**. Oxidative scission of both carbon–carbon double bonds in **17** with ozone, followed by two straightforward operations, furnishes intermediate **38**. The stability of the oxime in these systems is noteworthy, and is attributed to its hindered nature. At this juncture, it is instructive to note that substituted cyclopentene rings, like the



Scheme 5. The Woodward synthesis of β -cornnorsterone (**14**).

one present in **17**, can be regarded as latent cyclohexenones; the application of oxidative cleavage and aldol cyclodehydration reactions can accomplish the conversion of a substituted cyclopentene nucleus into a cyclohexenone. Although oxidative scission of the cyclopentene ring in **17** provides a methyl ketone at both ends of the point of cleavage, it is possible to selectively convert the less hindered of the two methyl ketones in **38** into an enamine with pyrrolidinium acetate. The close spatial relationship between the nucleophilic enamine grouping and the electrophilic, but hindered, methyl ketone function in **39** favors the desired cyclodehydration reaction leading to **40**. Mesylation of the oxime hydroxyl in **40**,

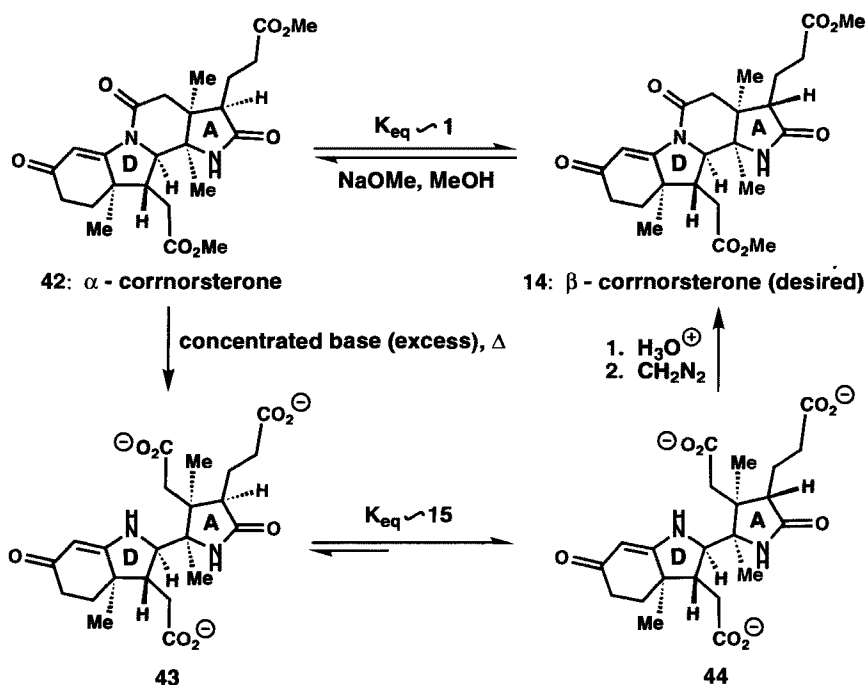


followed sequentially by ozonolysis of the enone double bond, treatment with periodic acid, and esterification with diazomethane, provides compound **15**.

Although it was anticipated all along that the latent reactivity of the oxime could be unveiled in a Beckmann rearrangement, the dramatic productivity of the next reaction was not. When a solution of **15** and polystyrenesulfonic acid in methanol is heated to 170 °C, several useful transformations take place (see intermediate **41**). As expected, the Beckmann rearrangement proceeds in the desired way to give a six-membered lactam ring. Located only five atoms away from the lactam nitrogen atom is the electrophilic carbonyl group of the methyl ketone, and only four atoms intervene between the ketone methyl group and the electrophilic ester carbonyl. Under these conditions, and owing to the proximity of these reactive groups, the lactam nitrogen cannot resist attacking the neighboring carbonyl group (the aldol reaction may precede the Beckmann rearrangement). Methanol and water are expelled during this remarkable transformation giving α - and β -cornnorsterone, compounds **42** and **14**, respectively.

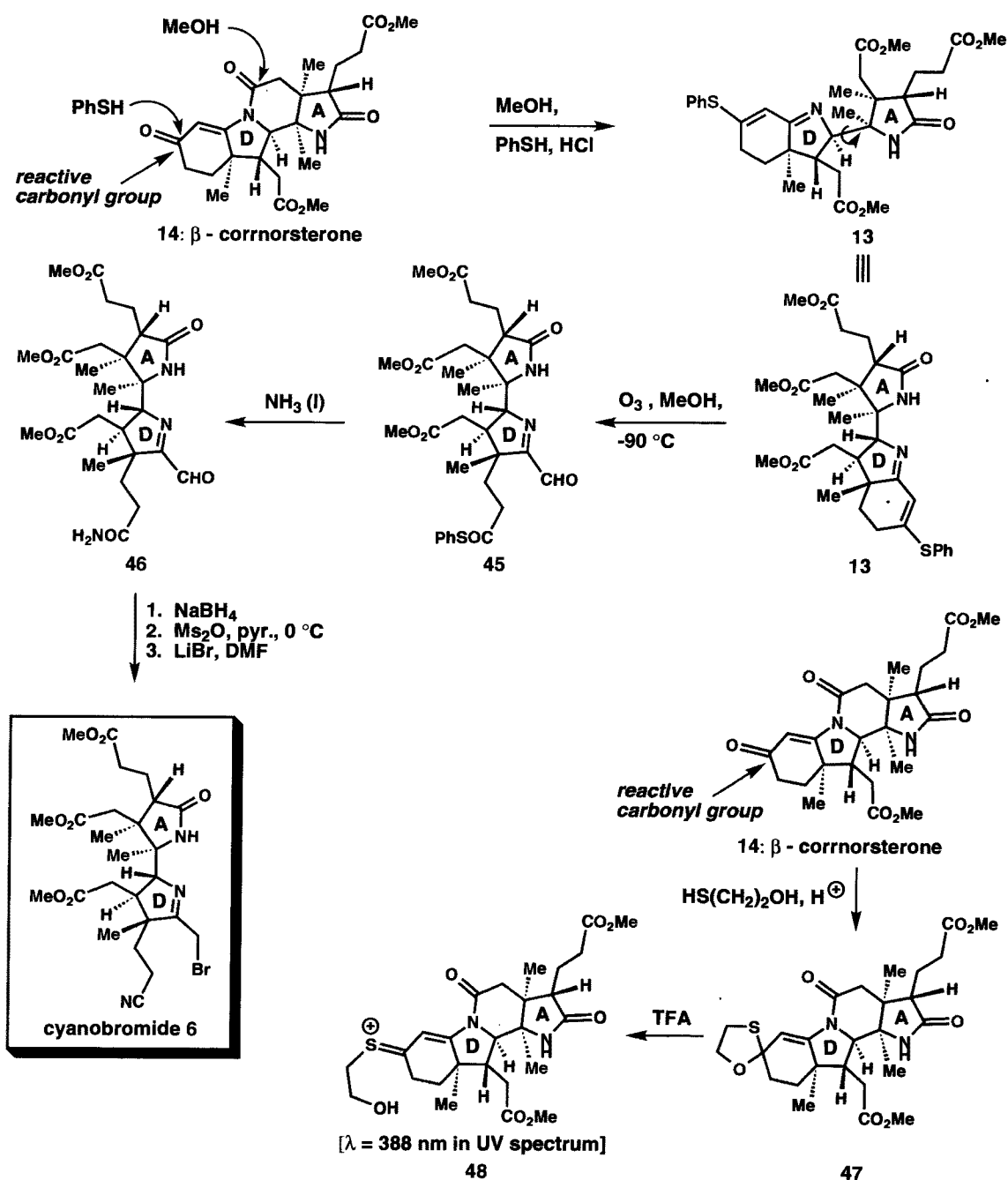
α -Cornnorsterone (**42**), the undesired diastereoisomer, is by far the major product formed in the acid-catalyzed transformation of oxime mesylate **15**. The configuration of the methyl propionate-bearing stereocenter constitutes the only difference between **42** and **14**. It was observed at an earlier stage in the synthesis that the action of alkaline reagents on pentacyclenone (**18**) results in facile cleavage of its six-membered lactam ring. Under the same conditions, however, a very similar six-membered lactam in **42** was found to resist hydrolysis. It was reasoned that if α -cornnorsterone's lactam ring were to be opened, then the resultant acetate chain would occupy a much larger volume of space relative to the lactam ring. This would introduce significant destabilizing steric interactions with the proximal propionate chain. Thus, to avoid such interactions, α -cornnorsterone need only resist hydrolysis. An important breakthrough in the synthesis was achieved when α -cornnorsterone (**42**) was treated with a large excess of concentrated base (Scheme 6). Under these conditions, the six-membered lactam ring in **42** is cleaved, and the stereogenic center next to the A-ring amide carbonyl is epimerized. The equilibrium between compounds **43** and **44** in Scheme 6 is shifted strongly in favor of **44**. Acidification of the reaction mixture, followed by treatment with diazomethane furnishes pure β -cornnorsterone (**14**) in 90 % yield together with 6 % of recyclable α -cornnorsterone. Interestingly, direct equilibration of the stereoisomeric cornnorsterones using methoxide ion in dry methanol provides a 1:1 mixture of the two substances (Scheme 6).

In β -cornnorsterone (**14**), we have an intermediate that possesses all six contiguous stereogenic centers occupying the left-hand portion of vitamin B₁₂. Scheme 7 presents the straightforward and elegant sequence of reactions that led to the synthesis of cyanobromide **6**, and the observations that formed the basis for this



Scheme 6. Base-induced conversion of **42** to **14**.

expedient route. The carbonyl group highlighted by the arrow is part of an unusual β -acylamino α,β -unsaturated system and is, therefore, rather reactive. During the course of studies relevant to the chemistry of β -cornnorsterone (**14**), it was observed that this reactive carbonyl group can be readily converted into hemithioketal **47** (see lower right-hand portion of Scheme 7). What is very interesting is that in the presence of trace quantities of trifluoroacetic acid, a strikingly intense long-wavelength absorption at 388 nm is observed in the UV spectrum. Such an absorption is characteristic of the unusual acylamino α,β -unsaturated thioketone onium salt present in **48**. This experiment demonstrates that the carbon-oxygen bond of the hemithioketal moiety is cleaved selectively in the presence of acid. An oxonium ion intermediate, which would have formed in the event that the carbon-sulfur bond had cleaved, could not be detected spectroscopically; its presence would have been revealed by a characteristic absorption at 325 nm. The implication of this experiment is that it should be possible to maintain a carbon-sulfur bond at that position while creating a carbon-oxygen bond in another position. In a most impressive transformation, treatment of β -cornnorsterone (**14**) with HCl and a mixture of methanol and thiophenol results in the completely selective attack upon the δ -lactam carbonyl by a molecule of methanol, and the completely selective addition of the thiophenol to the reactive car-



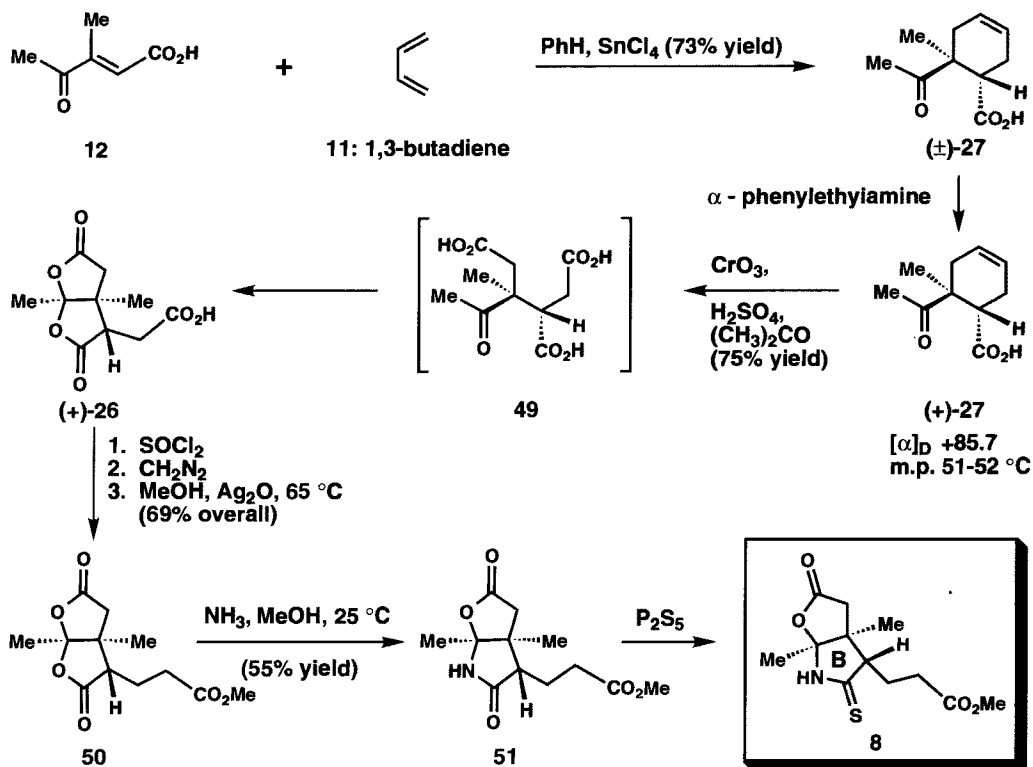
Scheme 7. The Woodward synthesis of cyanobromide 6.

bonyl group to give **13** (Scheme 7). When redrawn, the homology between intermediate **13** and the left wing of vitamin B₁₂ is obvious. Although the ozonolytic cleavage of the vinyl sulfide function in **13** proceeds efficiently and gives **45**, this reaction deserves comment. A step earlier, we learned that, under acidic conditions, the combined action of methanol and thiophenol on β -cornnorsterone (**14**) results in the smooth formation of compound **13**. This reaction is, as it turns out, very general; a variety of thiols can be substituted for thiophenol to produce compounds very similar to **13**. Unfortunately, however, when ethane-, methane-, 2-methyl-2-propane-, or phenylmethanethiol is used, the subsequent ozonolysis reaction produces significant quantities of a sulfur oxidation by-product. Only in the case of thiophenol does the ozonolysis reaction proceed cleanly and in the desired way to give the formyl thioester (i.e. **45**).

Contained within **45** is one side chain that terminates in a phenylthioester group. It was known, at the time, that whereas oxygen-based nucleophiles react with esters and thioesters with roughly equal facility, nitrogen-based nucleophiles react more readily with thioesters. Thus, treatment of **45** with liquid ammonia results in the completely selective replacement of the thiophenol grouping by ammonia to give formyl amide **46** in nearly quantitative yield. Although the inherently reactive aldehyde grouping in **45** is remarkably impervious to the action of liquid ammonia, it is readily reduced by sodium borohydride to the corresponding primary alcohol. Treatment of this substance with methanesulfonic anhydride and pyridine, followed by displacement of the resulting mesylate with bromide ion, completes the synthesis of cyanobromide **6**, a suitably differentiated left-wing building block. It is important to note that the employment of methanesulfonic anhydride in this sequence is not arbitrary; the use of the more conventional methanesulfonyl chloride or bromide to achieve the desired mesylation is attended by the production of significant amounts of a halide by-product. This complicating path can be easily circumvented through the use of methanesulfonic anhydride. It will also be noted that the terminal nitrile function in **6** is formed through dehydration of the primary amide grouping with methanesulfonic anhydride.

8.3.2 The Eschenmoser Synthesis of B-Ring Intermediate **8**

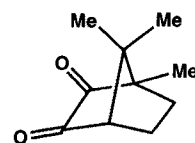
Scheme 8 presents the sequence of reactions that led to the synthesis of the B-ring of vitamin B₁₂ by the Eschenmoser group. An important virtue of the Diels–Alder reaction is that it is a stereospecific process wherein relative stereochemical relationships present in the diene and/or the dienophile are preserved throughout the course of the reaction.⁸ Thus, when the doubly activated dienophile **12** (Scheme 8) is exposed to butadiene **11** in the presence of stannic chloride, a stereospecific reaction takes place to give compound **27** in racemic form. As expected, the *trans* relationship between



Scheme 8. The Eschenmoser synthesis of B-ring intermediate **8**.

the keto and carboxyl groups in **12** is reflected in Diels–Alder adduct **27**. The carboxyl group in **27** is an important feature because it provides a simple means whereby this compound can be resolved. Treatment of racemic (±)-**27** with optically active α -phenylethylamine gives a readily separable mixture of diastereomeric ammonium salts. Reconstitution of the enantiomeric carboxylic acids furnishes both in enantiomerically pure form. To reach vitamin B₁₂, it is the dextrorotatory carboxylic acid (+)-**27** which is required. Oxidative cleavage of the carbon–carbon double bond in (+)-**27** with chromic acid produces an intermediate with a carboxyl group on both sides of the point of cleavage (see **49**). The spatial proximity of two of the three carboxyl groups and the ketonic carbonyl group results in a facile intramolecular reaction to give dilactone (+)-**26**. Arndt–Eistert homologation¹¹ of the acetic acid side chain in (+)-**26** furnishes the dilactone propionic ester **50**. The selective formation of lactam **51** when dilactone **50** is treated with ammonia is very interesting. Although ammonia reacts with both lactonic carbonyl groups indiscriminately, it is possible to achieve the selective formation of the desired lactam **51** through a simple

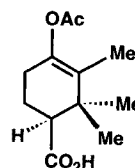
equilibration process. The selective action of phosphorus pentasulfide (P_2S_5) on lactam **51** affords enantiomerically pure thiolactam **8**, a latent electrophile representing the B-ring of vitamin B₁₂.



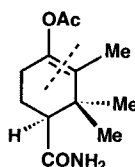
10: (+)-camphorquinone

8.3.3 The Woodward Synthesis of C-Ring Intermediate 9

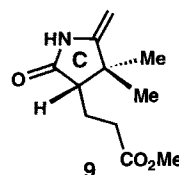
It was known from the work of Manasse and Samuel that a trimethylcyclohexanone carboxylic acid is formed when camphorquinone (**10**, Scheme 9) is exposed to acidic reagents. Subsequent studies by Simonsen and Chakravarti revealed the structure of the trimethylcyclohexanone carboxylic acid, and it was Cornforth¹² who recognized the structural relationship between this substance and ring C of vitamin B₁₂. In the face of such precedent, the approach to the C-ring building block logically begins with an acid-induced conversion of (+)-camphorquinone (**10**) into enantiomerically pure carboxylic acid **52** (Scheme 9). This interesting BF_3 -induced skeletal reorganization presumably proceeds through the cascade of reactions illustrated in Scheme 9. Sequential treatment of carboxylic acid **52** with oxalyl chloride and ammonia furnishes amide **53** and sets the stage for an unusual ozonolysis reaction. Oxidative cleavage of the enol acetate in **53** (dotted line) with ozone affords a mixed anhydride at one terminus and a ketone oxide at the other. This mixed anhydride is, of course, quite electrophilic, and it suffers attack by the primary amide nitrogen to give a succinimide. One of the carbonyl groups of the succinimide is suitably disposed with respect to the ketone oxide, and an intramolecular cycloaddition reaction takes place to give the observed product **54** (see presumed mechanism in Scheme 9). Reduction of **54** with zinc in methanol gives keto succinimide **55**. Treatment of **55** with methanolic hydrogen chloride results in the formation of **56**, which, when pyrolyzed, gives unsaturated lactam **9**, a latent nucleophile representing ring C of vitamin B₁₂.



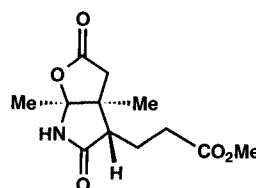
52



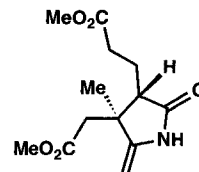
53



9



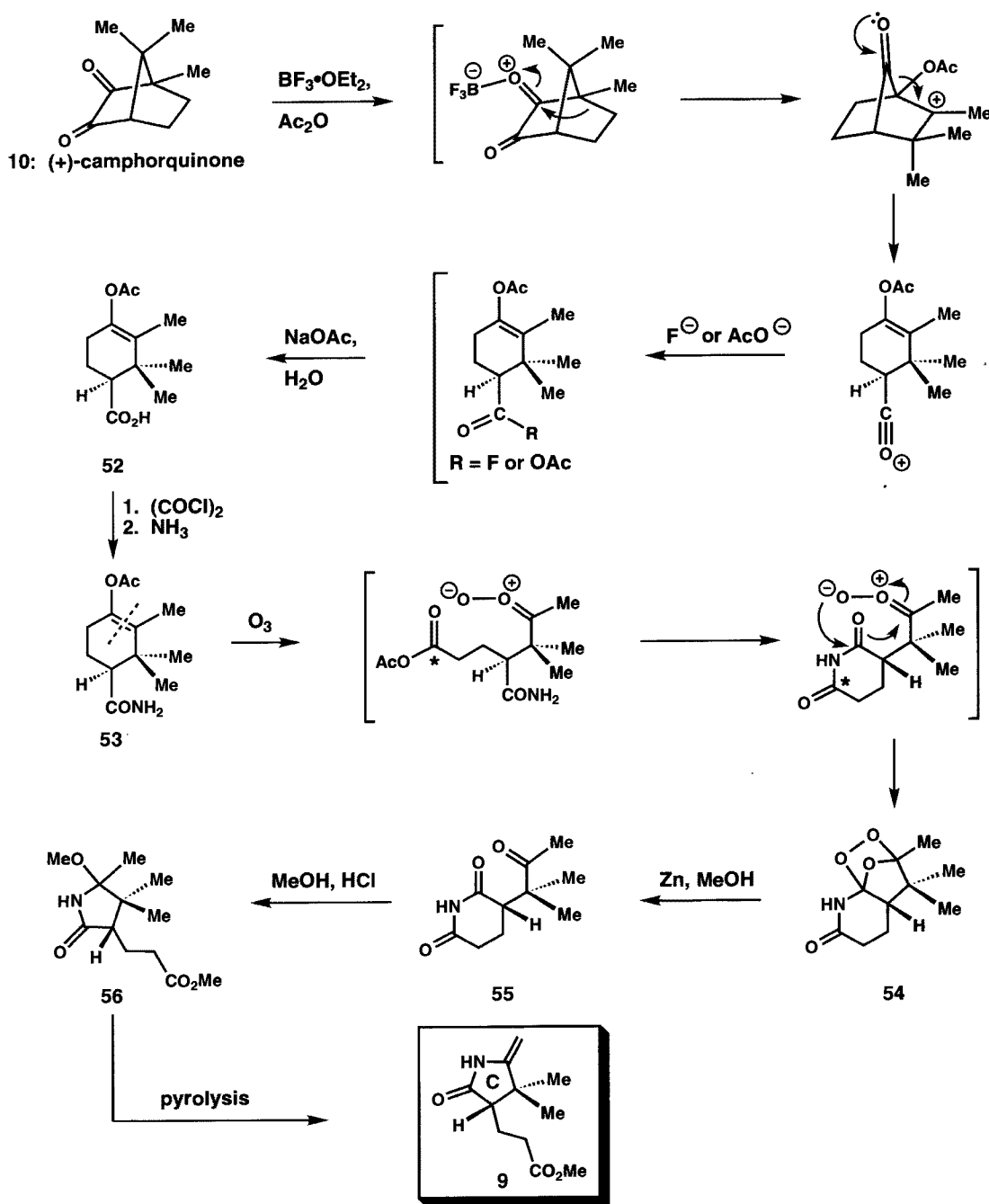
51

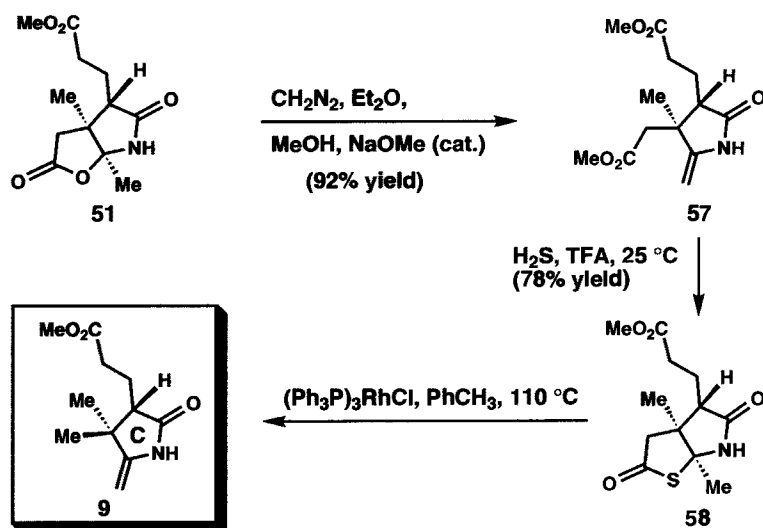


57

8.3.4 The Eschenmoser Synthesis of C-Ring Intermediate 9

From intermediate **51** (Scheme 10), the precursor of B-ring intermediate **8**, the Eschenmoser synthesis of the C-ring building block requires only three synthetic steps. Treatment of **51** with diazomethane and a catalytic amount of sodium methoxide in a mixture of ether and methanol leads to the formation of intermediate **57**. In the presence of sodium methoxide, the amide hydrogen in **51** is removed as a proton, and the delocalized anion thus formed initiates opening of the γ -lactone ring. Esterification of the liberated acetic acid side chain with diazomethane and simple enamide tautomerization then gives intermediate **57**. When **57** is treated with hydrogen sulfide and trifluoroacetic acid, a new thiolactone ring is formed, and the bicyclo[3.3.0]octane

**Scheme 9.** The Woodward synthesis of C-ring intermediate **9**.

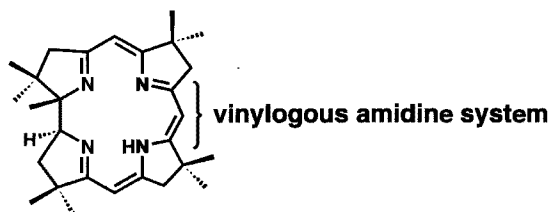


Scheme 10. The Eschenmoser synthesis of C-ring intermediate **9**.

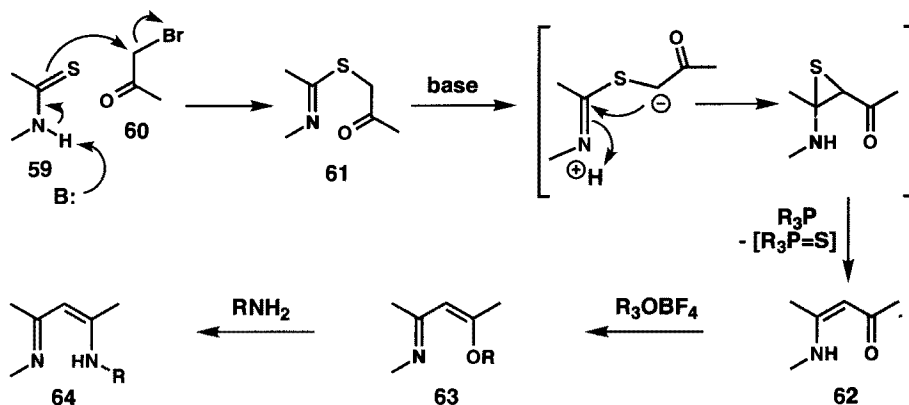
framework is reconstituted, giving intermediate **58**. In refluxing toluene solution and in the presence of Wilkinson's catalyst, **58** is transformed into C-ring intermediate **9**. Although the Eschenmoser synthesis of the C-ring building block is only three steps from an intermediate already being used for the preparation of the B-ring of vitamin B₁₂, both groups found the camphor-based route summarized in Scheme 9 to be more preparatively useful.

8.3.5 The Eschenmoser Synthesis of Thiodextrolin (7)

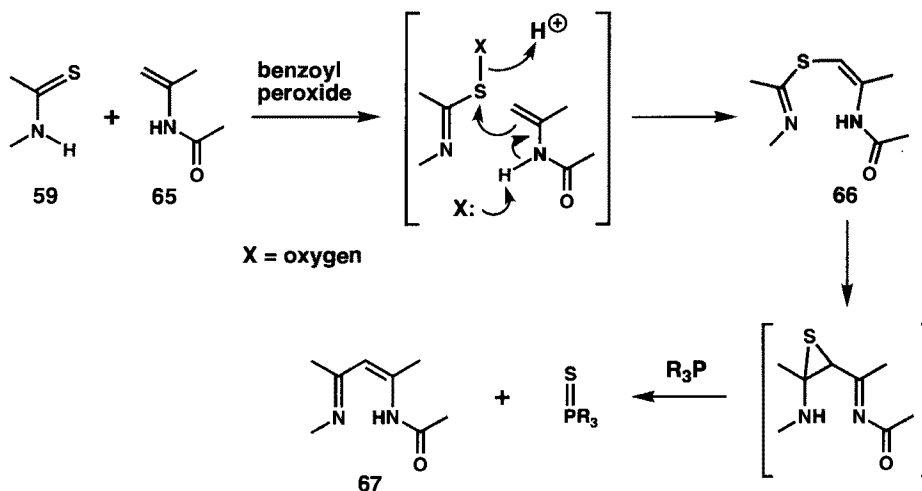
It is instructive to digress at this point. Inherent in any venture with the synthesis of a corrin as its objective is the challenge of constructing the vinylogous amidine system, the characteristic structural unit of the corrin chromophore (see Scheme 11). On its own, the vinylogous amidine system is simply the diaza analogue of the β -keto enol system, a grouping that is very familiar and very accessible. However, in the context of a corrin chromophore, the vinylogous amidine system can present a significant synthetic challenge. During the course of extensive model studies relevant to the synthesis of vitamin B₁₂, Eschenmoser and his group at ETH developed a very elegant and general method for the synthesis of vinylogous amidines which has had a lasting influence on the corrin field. The method is known as the Eschenmoser sulfide contraction reaction,⁷ and its development was motivated by a very important principle in organic synthesis which is enunciated in the following quotation by Eschenmoser: "Whenever in the synthesis of complex organic molecules one is confronted with a situation where the suc-



The sulfide contraction method via alkylative precoupling



The sulfide contraction method via oxidative precoupling



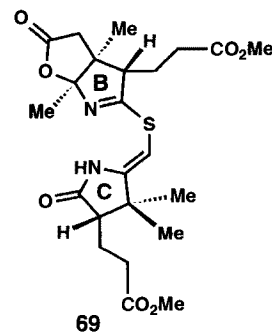
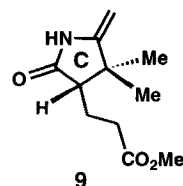
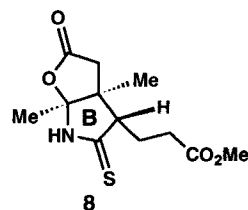
Scheme 11. The Eschenmoser sulfide contraction.

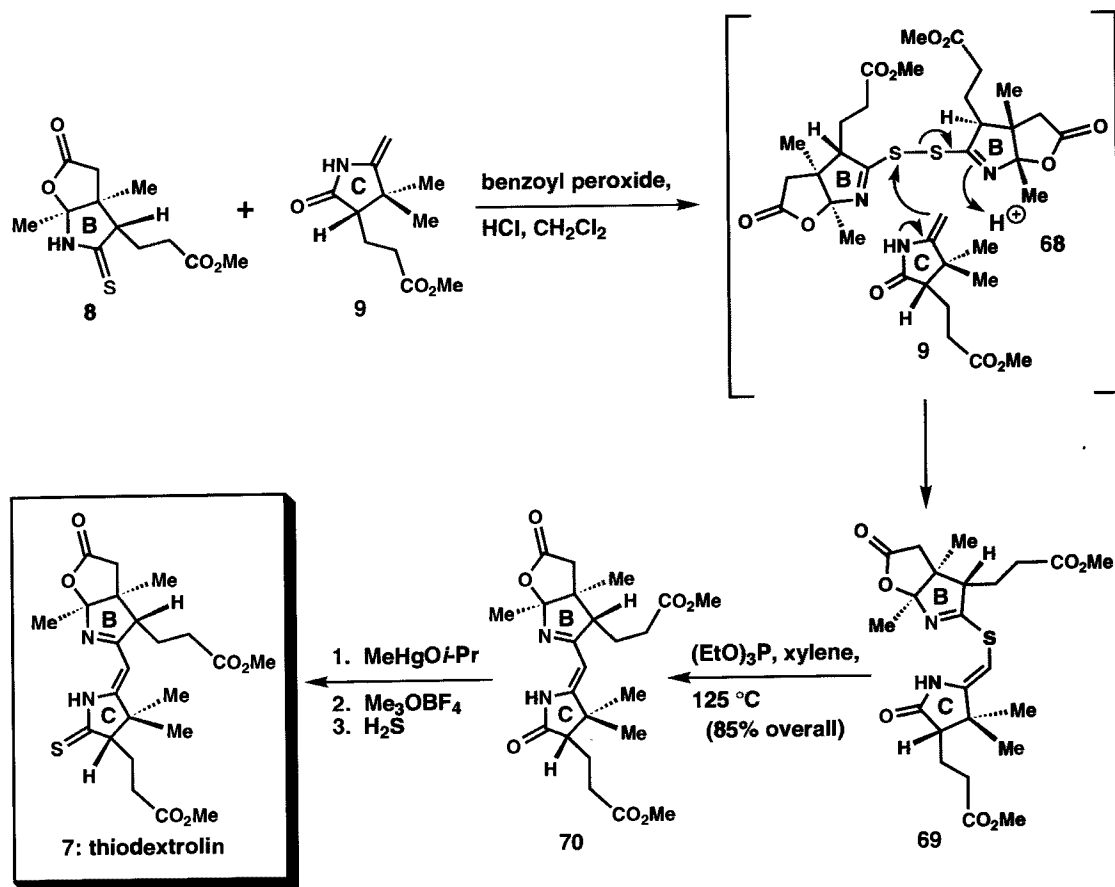
cess of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look out for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly.”^{7d}

The key features of both alkylative and oxidative versions of the Eschenmoser sulfide contraction are presented in Scheme 11. In both versions, one of the two coupling partners is a thioamide. In the alkylative Eschenmoser sulfide contraction, the nucleophilic sulfur atom of generic thioamide **59** initiates an S_N2 displacement of a suitable leaving group (i.e. the bromide in intermediate **60**) to give thioiminoester **61**. In the presence of an enolizing base, the nucleophilic character of the carbon atom situated between the sulfur atom and the carbonyl group in **61** is unveiled, and it obligingly attacks the proximal electrophilic thioiminoester carbon (see arrows). It is presumed that this event leads to the formation of an episulfide which subsequently collapses in the presence of a phosphine or a phosphite thiophile to give vinylogous amide **62**. O-Alkylation of **62** with a trialkyloxonium salt (Meerwein's salt), followed by treatment with an amine, leads to the formation of vinylogous amidine system **64**. The latter transformation (**63** \rightarrow **64**) can be formulated as a Michael addition/elimination reaction.

In the oxidative Eschenmoser sulfide contraction (Scheme 11), thioamide **59** is oxidized by benzoyl peroxide to give either a symmetrical disulfide or the *O*-benzoate of the thiolactam-*S*-oxide. In any event, the once-nucleophilic thioamide sulfur atom is now forced to adopt the role of electrophile; a reactivity umpolung has, in effect, been achieved.¹³ The nucleophilic enamide **65** attacks the sulfur atom leading to the formation of sulfur-bridged intermediate **66**. The action of a phosphine or a phosphite thiophile on the putative episulfide then gives vinylogous amidine **67**.

Schemes 8 through 10 describe the syntheses of two key intermediates representing rings B and C. We now have the good fortune to witness the elegant means by which these intermediates were combined to give the entire right-wing portion of vitamin B₁₂ (see Scheme 12). When a solution of the thiolactam **8** and the enamide **9** in CH₂Cl₂ is treated with benzoyl peroxide and a catalytic amount of hydrogen chloride, the sulfur-bridged compound **69** is formed. In this most interesting reaction, the thiolactam moiety in **8** is oxidized with benzoyl peroxide to give bisimidoyl disulfide **68** which reacts with enamide **9**, in the expected way, to give **69**. In this reaction, a new carbon-sulfur bond is created at the expense of a weak sulfur-sulfur bond, while an equivalent of thiolactam **8** is returned to the reaction. The carbon-sulfur bond contained within intermediate **69** is a valuable structural feature. Its existence is transient but nevertheless crucial to the success of the synthesis of thiodextrolin (**7**); it permits the union of rings B and C of vitamin B₁₂ by bringing into proximity the two carbon atoms between which a bond must be formed. When a solution of **69** in xylene is heated in the presence of the thiophile triethylphosphite, the sulfur atom,



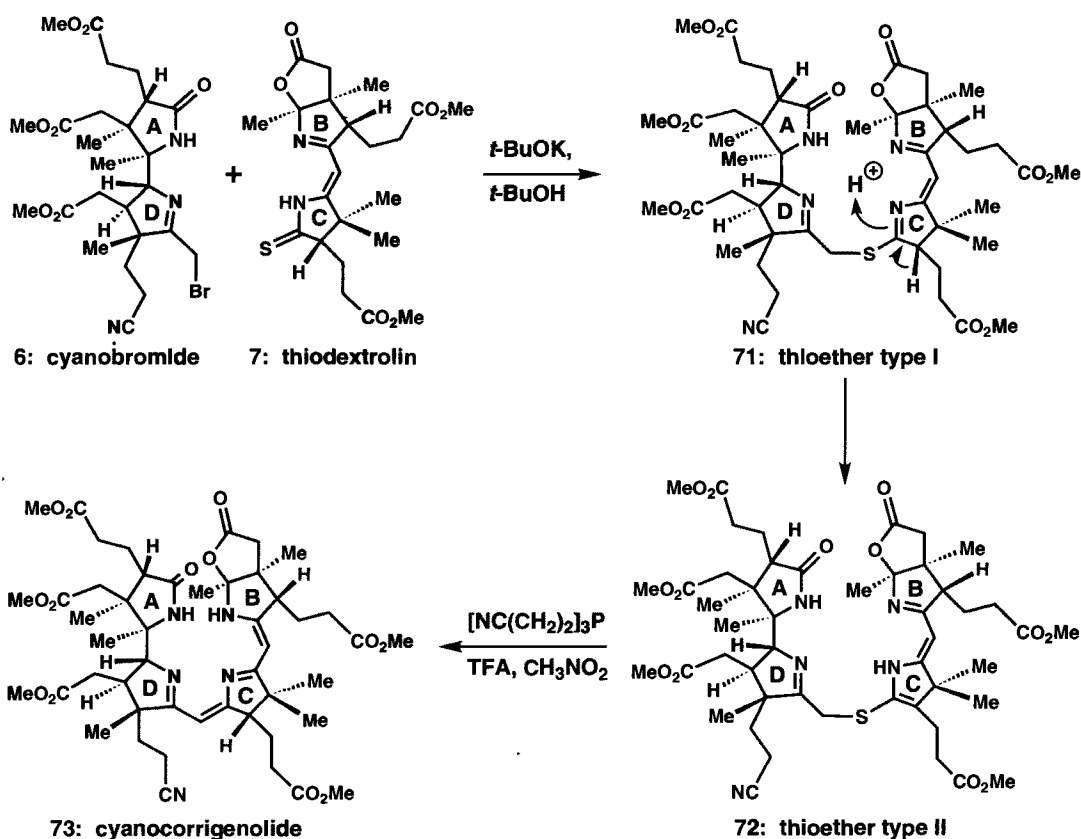


Scheme 12. The Eschenmoser synthesis of thiodextrolin (**7**).

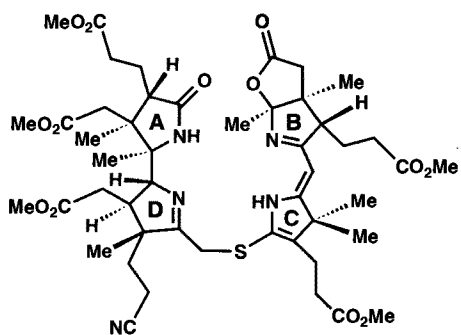
which facilitates the carbon–carbon bond forming event by making it intramolecular, is removed to give intermediate **70**. Although the mechanistic details of this reaction were not examined, the formation of a transitory episulfide which is subsequently collapsed by triethylphosphite is presumed. The completion of the synthesis of thiodextrolin (**7**) only requires the selective conversion of the amide function in **70** into a thioamide. To accomplish this task, the methylmercury complex of the free amide in **70** is prepared first. This provides sufficient activation of the amide grouping, and allows a smooth and specific O-alkylation with Meerwein's salt. Exposure of the resulting iminomethylester to hydrogen sulfide then gives thiodextrolin (**7**). The synthesis of the right-wing portion, the B–C sector, of vitamin B₁₂ is now complete.

8.3.6 The Woodward–Eschenmoser Macrocyclization Strategy

We have now reached a pivotal stage in the synthesis. We have retraced the elegant sequences of reactions that have led to syntheses of both the left- and right-wings of vitamin B₁₂ in their correct absolute stereochemical forms. We are now in a position to address the union of cyanobromide **6** and thiodextrolin (**7**) (see Scheme 13). The reactivity potential of these two molecules complement each other. Cyanobromide **6** is, in its most basic form, an alkylating agent, albeit a very elaborate one. Thiodextrolin (**7**), on the other hand, is a nucleophile by virtue of the presence within its structure of the thioamide group. Under carefully controlled conditions and in the presence of potassium *tert*-butoxide, it is possible to bring about a quantitative union of intermediates **6** and **7** through the formation of a carbon–sulfur bond. In the event, the thioamide proton in **7** is removed by a base to give a nucleophilic thiolate ion which subsequently attacks the bromine-bearing carbon in **6** in an intermolecular S_N2-type reaction. The product formed from the direct



Scheme 13. The Woodward–Eschenmoser A–B cyclization strategy.

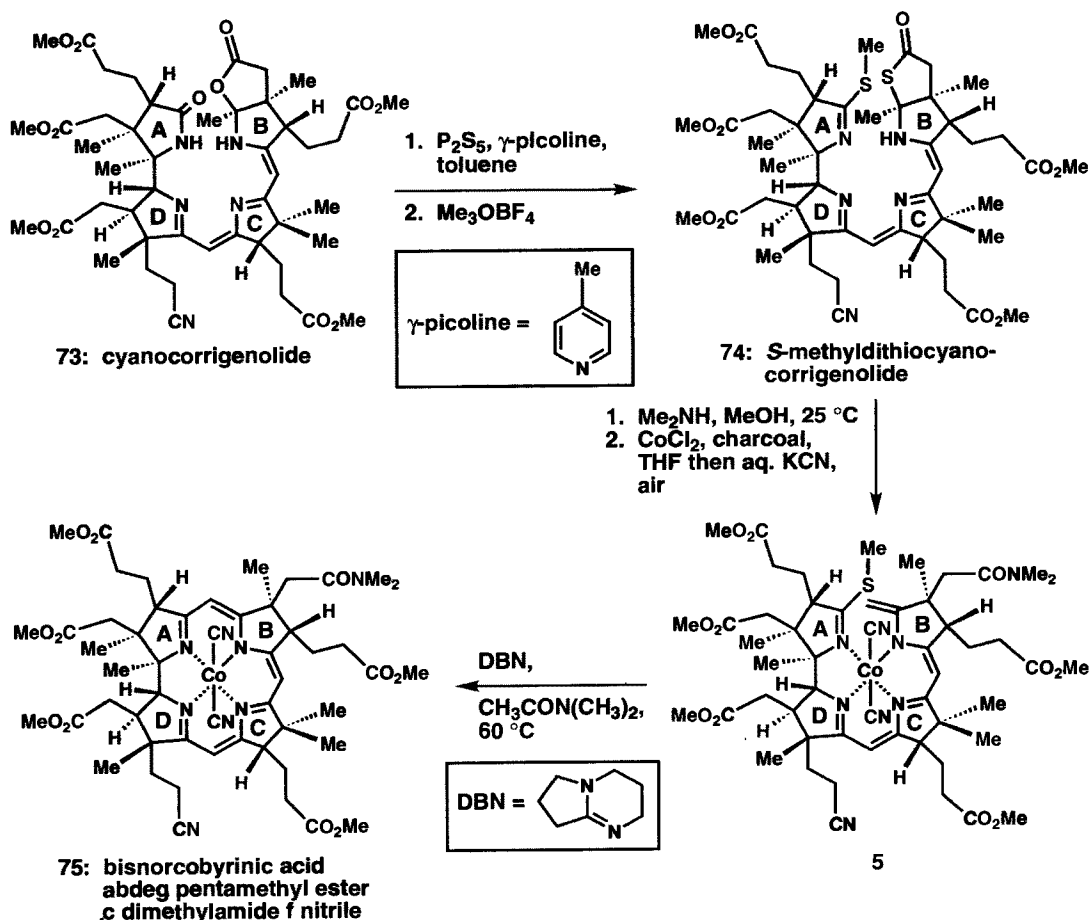


72: thioether type II

union of **6** and **7** is referred to as thioether type I, intermediate **71**. Upon purification and under a variety of conditions, it was found that this substance undergoes ready conversion to a closely related substance, thioether type II, intermediate **72**. This facile and seemingly sinister transformation destroys the stereocenter in ring C, and it presented a formidable stumbling block on the road to vitamin B₁₂. Although many attempts to join the A–D and B–C sectors in **72** through a carbon–carbon bond were completely unsuccessful, it was discovered that the combined action of tris- β -cyanoethylphosphine and trifluoroacetic acid (TFA) on **72** effects a smooth conversion to cyanocorrigenolide (**73**). In this reaction, it is presumed that the C-ring iminothioether is reconstituted, thereby setting the stage for the Eschenmoser sulfide contraction. As in the synthesis of thiodextrolin (**7**), the sulfur atom in **72** serves as a temporary bridge between the A–D and B–C sectors; it brings the two relevant carbon atoms together in space and allows the bond-forming process to proceed intramolecularly. After sulfur extrusion, cyanocorrigenolide (**73**) is obtained.

In **73**, we have an intermediate that contains both halves of vitamin B₁₂. Before the synthesis of the corrin nucleus can be addressed, **73** must be converted into a form amenable to cyclization. The conversion of the lactam carbonyl in ring A into a thio-carbonyl and the concomitant conversion of the lactone attached to ring B into a thiolactone can be achieved with phosphorus pentasulfide (see Scheme 14). Selective alkylation of the thiolactam sulfur atom in ring A with trimethyloxonium tetrafluoroborate then furnishes *S*-methylthiocyanocorrigenolide (**74**). Exposure of **74** to dimethylamine in methanol results in smooth cleavage of the thiolactone ring to give a dimethylamide at one terminus and a carbon atom which is now part of an exocyclic methylene group at the other terminus. Direct treatment of this labile intermediate with cobalt chloride in THF then furnishes intermediate **5**.

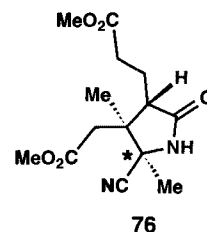
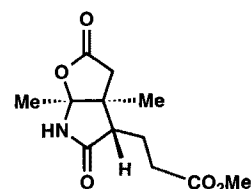
The stage is now set for the crucial cyclization event. There are three structural features contained within **5** that are vital to this transformation. First, the exocyclic methylene in ring B is special because it is expressed in the form of an enamine, and it is therefore nucleophilic. Second, the iminothioester in ring A possesses electrophilic potential that compliments the B-ring enamine. Third, the central cobalt atom preorganizes the structure of the secocorrin in a way that should facilitate the cyclization event. When a solution of **5** in dimethylacetamide is treated with diazabicyclononane (DBN) at 60 °C, the key intramolecular cyclization reaction takes place and furnishes compound **75** in high yield (Scheme 14). In this reaction, a new carbon–carbon bond linking rings A and B is formed and the methylthio group is displaced.

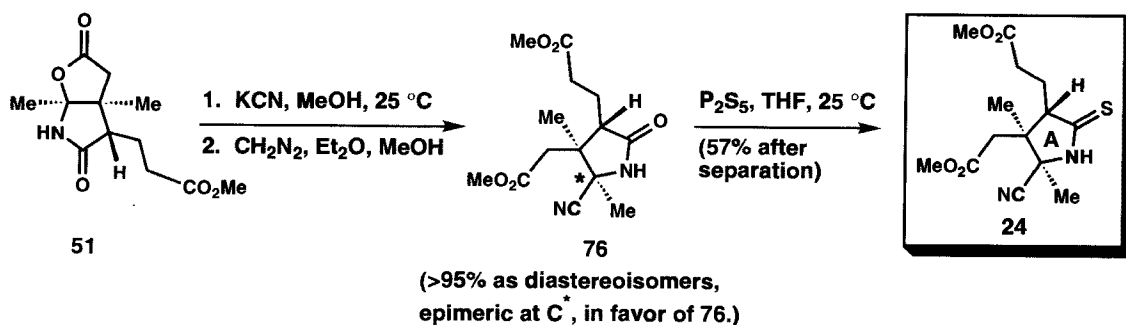


Scheme 14. The Woodward synthesis of intermediate **75**.

8.3.7 The Eschenmoser Synthesis of A-Ring Intermediate **24** and D-Ring Intermediate **25**

Schemes 15 and 16 summarize the syntheses of intermediates that represent rings A and D of vitamin B₁₂ by the Eschenmoser group. Treatment of lactam/lactone **51**, the precursor to B-ring intermediate **8** (whose synthesis has already been described, see Scheme 8), with potassium cyanide in methanol induces cleavage of the γ -lactone ring and furnishes intermediate **76** after esterification of the newly formed acetic acid chain with diazomethane. Intermediate **76** is produced as a mixture of diastereomers, epimeric at the newly formed stereocenter, in a yield exceeding 95%. Selective conversion of the lactam carbonyl in **76** into the corresponding thiolactam



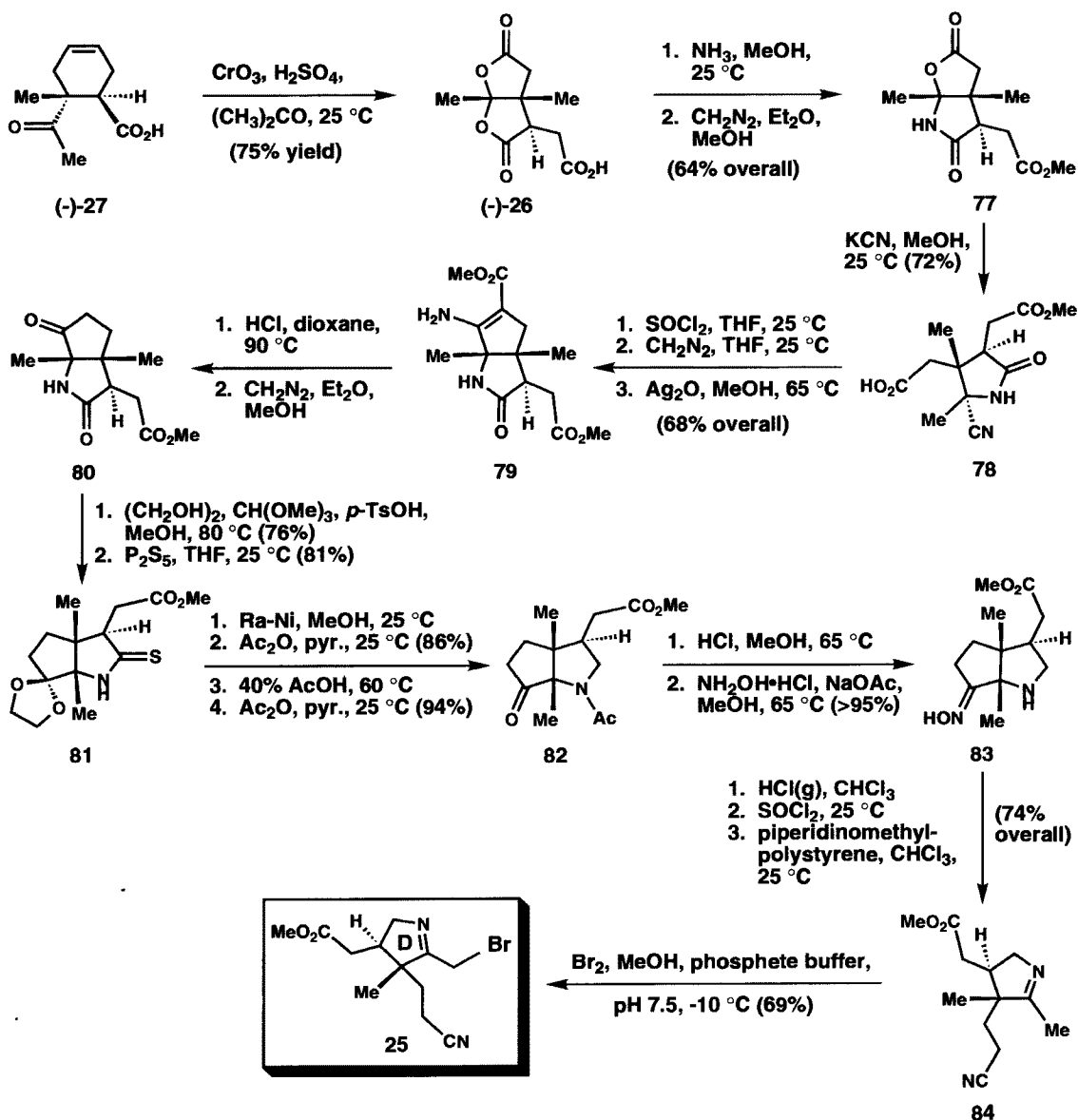


Scheme 15. The Eschenmoser synthesis of A-ring intermediate **24**.

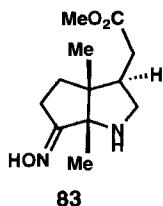
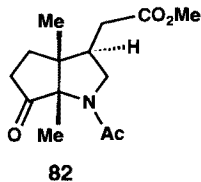
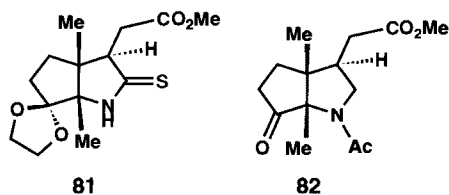
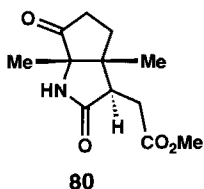
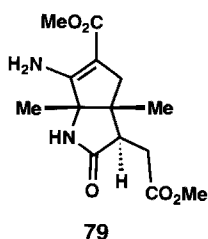
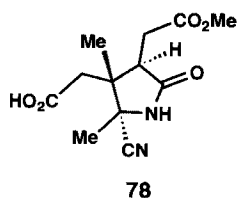
with P₂S₅ completes the synthesis of intermediate **24**, an appropriately functionalized representative of the A-ring of vitamin B₁₂.

The path to D-ring intermediate **25** starts with levorotatory carboxylic acid (–)-**27** (see Scheme 16). This molecule is one enantiomer of a substance readily assembled in racemic form from a Diels–Alder reaction between butadiene (**11**) and β-methyl-β-acetylacrylic-acid (**12**), and it is easily obtained in stereochemically pure form through a resolution of the racemate with enantiomerically pure α-phenylethylamine (see Scheme 8). At this juncture, a digression is in order. Those engaged in the synthesis of complex organic molecules are frequently presented with situations requiring only one enantiomer of a compound that can be prepared easily in racemic form. Once the desired stereoisomer is obtained through resolution, it is common practice to discard the unwanted enantiomer. Although wasteful, this practice is certainly acceptable. Nevertheless, it is most gratifying when a carefully planned synthesis utilizes both enantiomers of a racemic starting material. Here, in the Eschenmoser approach to the synthesis of vitamin B₁₂, the two-mirror-image forms of a simple racemic starting material are used to assemble all four rings of the natural product, each in its correct absolute stereochemical form (see Scheme 2). It should also be noted that in the Woodward synthesis of cyanobromide **6**, the availability of the “unnatural” enantiomer of key intermediate **19** (Scheme 4) permitted the exploration of a number of alternative synthetic pathways for further advance. In fact, almost all of the transformations that were employed in the synthesis of the left-wing sector were first discovered using substances that belong to the enantiomeric or “unnatural” series. Thus, even though only one enantiomer of intermediate **19** was ultimately incorporated into the vitamin B₁₂ synthesis, the “unnatural” enantiomer of **19** was not really wasted!¹⁴

As in the synthesis of (+)-**26** (Scheme 8), treatment of (–)-**27** with chromic acid accomplishes oxidative scission of the carbon–carbon double bond, and provides (–)-**26** after an intramolecular bislactonization reaction (Scheme 16). By analogy to the conversion of **50** into **51** (see Scheme 8), treatment of (–)-**26** with ammo-



Scheme 16. The Eschenmoser synthesis of D-ring intermediate 25.



nia leads, through an equilibration process, to the formation of intermediate **77** after esterification of the acetic acid side chain with diazomethane. When a solution of **77** in methanol is treated with potassium cyanide, the γ -lactone ring is opened, and a molecule of hydrogen cyanide is incorporated giving intermediate **78**. The next three-step sequence of reactions is very interesting. After Arndt–Eistert homologation¹¹ of the acetic acid side chain in **78**, the active methylene group of the newly formed methyl propionate side chain condenses intramolecularly onto the cyano group. To be more precise, the propionate ester, in its enolic form, attacks the electrophilic carbon of the nitrile group intramolecularly to give intermediate **79**. The action of acid on **79** accomplishes the hydrolysis of the vinylogous amide and methyl ester groupings, and induces a decarboxylation reaction. Intermediate **80** is produced after reesterification of the acetic acid side chain adjacent to the lactam carbonyl with diazomethane. After protection of the ketone carbonyl in **80** in the form of a 1,3-dioxolane, the lactam carbonyl is smoothly and selectively converted into the corresponding thiocarbonyl group with P₂S₅ to give **81**. Complete reduction of the thiocarbonyl moiety in **81** with Raney nickel, followed sequentially by acetylation of the nitrogen atom, hydrolysis of the 1,3-dioxolane, and reacylation of the nitrogen atom, results in the formation of ketone **82**. Assembly of oxime **83** in two steps from **82** sets the stage for an interesting variant of the Beckmann fragmentation reaction.⁹ Treatment of **83** with gaseous hydrogen chloride, followed successively by thionyl chloride and piperidinomethylpolystyrene induces a Beckmann fragmentation and furnishes intermediate **84** in 74 % yield. Bromination of the allylic methyl group in **84** using bromine in buffered methanol solution completes the synthesis of D-ring intermediate **25**.

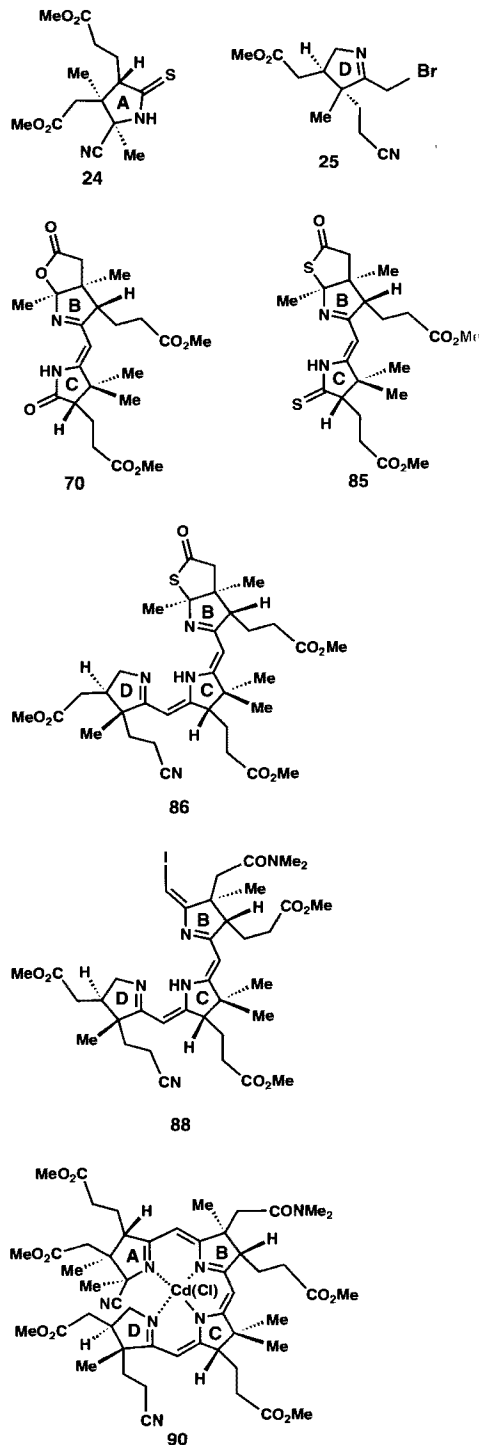
8.3.8 The Eschenmoser Cyclization Strategy

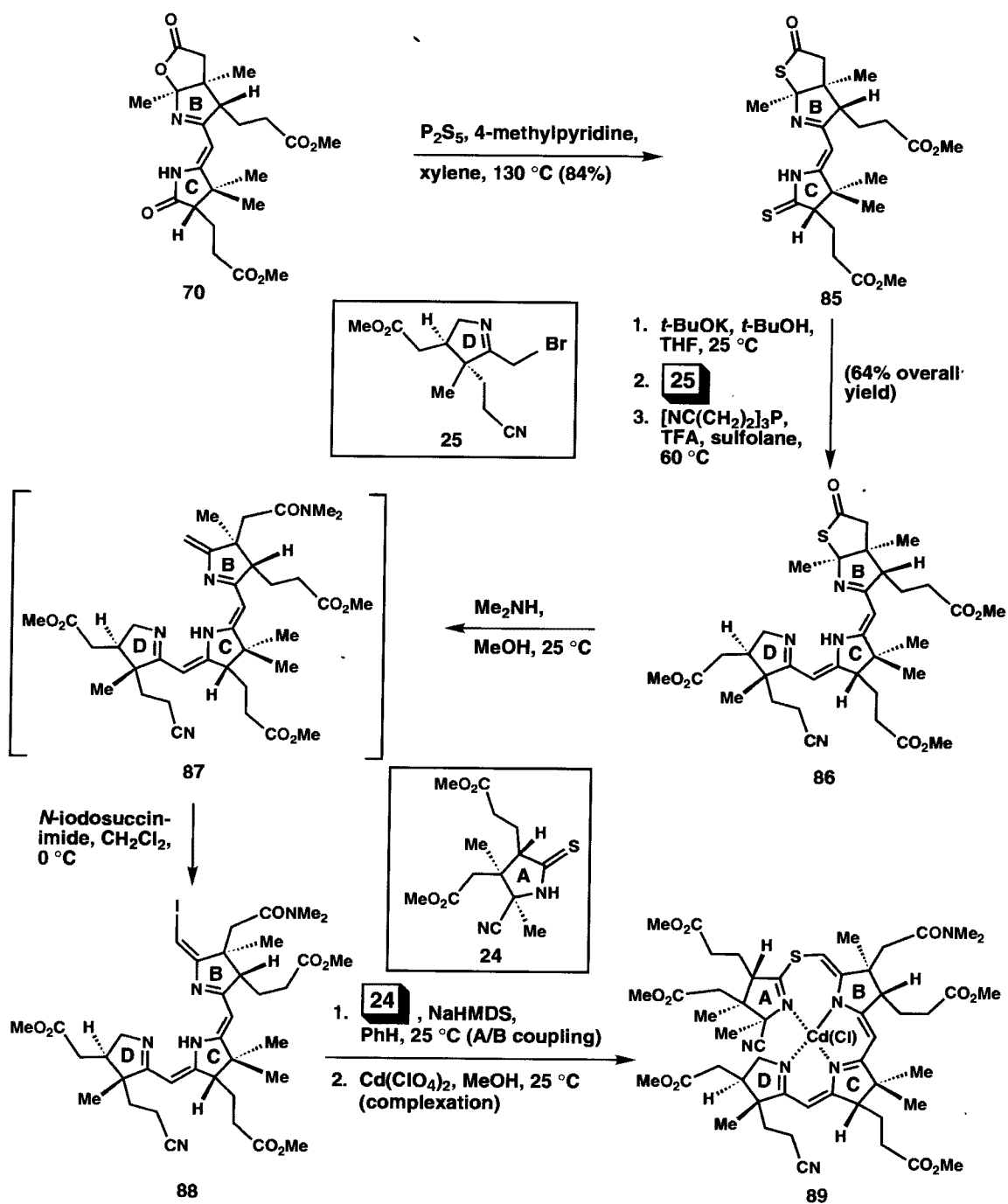
One of the crowning achievements that emanated from the total synthesis of vitamin B₁₂ was the development of the principles of orbital symmetry conservation by R.B. Woodward and R. Hoffmann.³ In Cambridge, MA, it was the observations made during the synthesis of the left-wing of vitamin B₁₂ that provided the seeds for this new theoretical advance, and, in Zürich, it was the recognition by Eschenmoser that a new approach to the synthesis of the macrocyclic corrin nucleus of vitamin B₁₂ could provide a stringent test of a theoretical prediction made by the Woodward–Hoffmann rules. It was under these circumstances that the A–D variant, the efficient and elegant contribution of the Eschenmoser group, was born.^{1d,6b,7d} The A–D variant subjects a secocorrin structure, which is organized in a helical fashion around a central metal atom, to visible light and accomplishes both the crucial macrocyclization reaction and the creation of the natural *trans* configuration at the junction between rings A and D (see Scheme 2). The recognition

that the four optically active building blocks representing rings A (**24**), B (**8**), C (**9**), and D (**25**) can be synthesized from the two enantiomers of a single starting compound is most impressive, and it seems to reflect underlying regularities in the biosynthesis of the natural corrinoids.^{7d} Schemes 17 and 18 present the synthetic details of this approach.

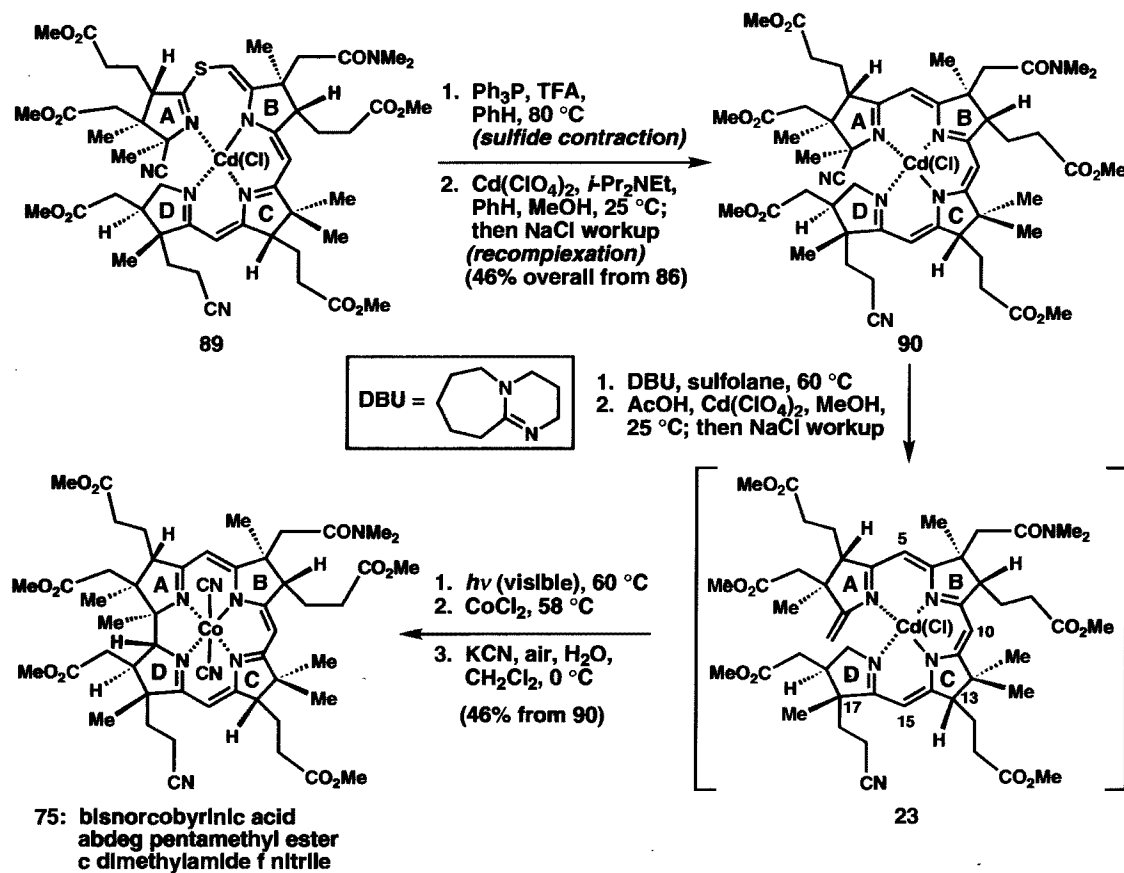
The Eschenmoser A–D variant begins with the conversion of intermediate **70**, the precursor of thiodextrolin (**7**), into the corresponding thiolactam thiolactone **85** with P_2S_5 . The sulfur atom of the thiolactam in **85** is to serve as a nucleophile in a coupling reaction with D-ring building block **25**. This reaction is analogous to the coupling of cyanobromide **6** with thiodextrolin (**7**) (see Scheme 13), a key operation in the Woodward/Eschenmoser A–B variant. Treatment of **85** with *tert*-butoxide produces a thiolate ion which subsequently displaces the ring D-bromide to give a sulfur-bridged intermediate. As we have already seen in analogous systems, the sulfur atom serves as a disposable tether; it forces rings C and D into neighboring regions of space and facilitates the key carbon–carbon bond forming event by making it intramolecular. After it has served its purpose, the sulfur atom is smoothly excised by the phosphine thiophile. In the presence of dimethylamine, intermediate **86** is converted into exocyclic enamine **87**. This intermediate is not isolated; it is treated directly with *N*-iodosuccinimide to give vinyl iodide **88**. By employing a modified sulfide contraction procedure,^{7c} the iodinated enamine **88** is coupled with the A-ring building block **24** to give, after complexation with cadmium, the sulfur-bridged complex **89**. On the basis of observations made during the synthesis of metal-free corphin derivatives,¹⁵ it is likely that metal complexation assists the subsequent sulfide contraction. Treatment of intermediate **89** (Scheme 18) with triphenylphosphine and trifluoroacetic acid induces sulfide contraction, giving intermediate **90** after recomplexation with cadmium.

In the Eschenmoser synthesis of A-ring intermediate **24** (see Scheme 15), a cyano substituent was introduced as a means of masking the strongly nucleophilic enamide double bond so that the thioamide function could adopt the role as nucleophile in the coupling reaction with intermediate **88**. Having served its purpose as a protecting group, the cyano substituent in intermediate **90** is eliminated in the presence of DBU giving, after recomplexation with cadmium, key intermediate **23**. The stage is now set for the crucial macrocyclization event. Secocorrin complex **23**, with its newly formed exocyclic methylene group, is not isolated; upon irradiation with visible light, it readily participates in an antarafacial sigmatropic 1,16-hydrogen shift from the methylene group in ring D to the exocyclic methylenide group in ring A, followed by an antarafacial electrocyclic 1,15 $\pi \rightarrow \sigma$ isomerization to corrin **75**. This reaction was studied in detail in the context of a simpler model system,^{6b,7d} and it is presumed that the path presented in Scheme 19 is taken. The rate-limiting step in this process is the photo-induced shift of a hydrogen atom from the D-ring methylene in **91** to the A-ring

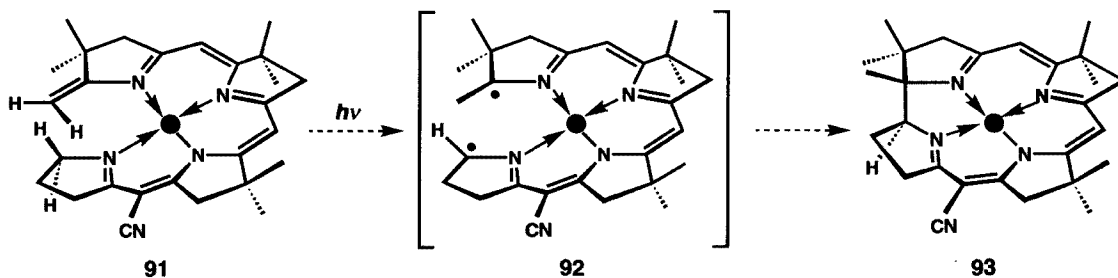




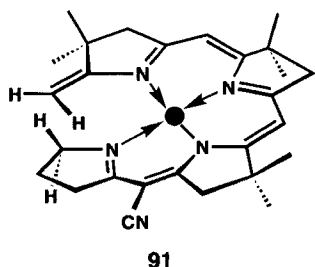
Scheme 17. The Eschenmoser A–D cyclization strategy.



Scheme 18. The Eschenmoser synthesis of intermediate **75**.



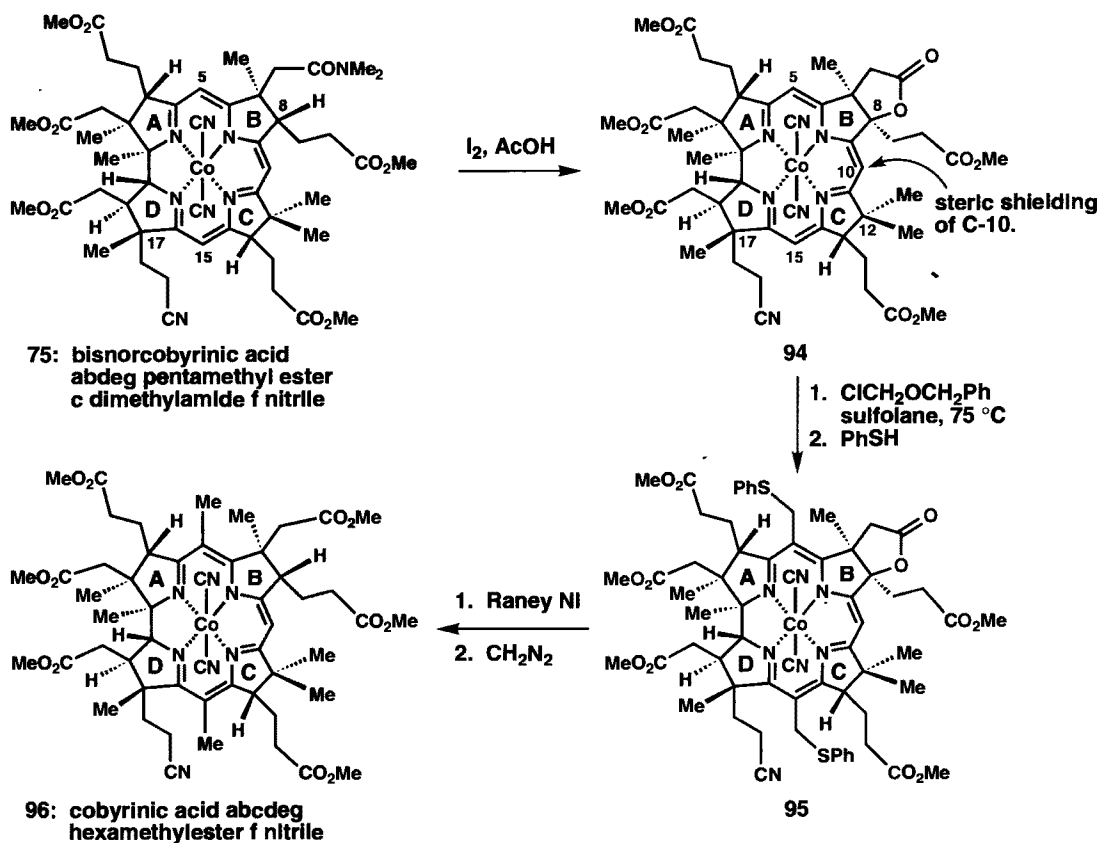
Scheme 19. Photochemical A–D cycloisomerization: presumed reaction path.



methyldene carbon sixteen atoms away. Studies carried out on the secocorrin palladium complex (**91**; ● = M = Pd) revealed that the cyclization displays an isotope effect of about 7 when the D-ring methylene hydrogens in **91** are replaced with deuteriums. Dunitz and his group at ETH contributed X-ray crystallographic results which revealed that the secocorrin structure (**91**; ● = M = CdCl) is coiled around the central metal atom in a helical manner.^{1d} The juxtaposition of the D-ring methylene group and the A-ring methyldene is a most gratifying consequence of such an arrangement; the helical arrangement of the secocorrin structure around the metal places the D-ring methylene group beneath (or above) the A-ring methyldene π system and guides the stereochemical course of the cycloisomerization event. Provided that the central metal ion is inert with respect to the quenching of the excitation of the chromophore, the photo-induced cycloisomerization proceeds very smoothly and provides corrin complexes possessing the necessary *trans* configuration between rings A and D. The *trans* A–D configuration found in cobyrinic acid (**4**) is thermodynamically more stable than the alternative *trans* configuration. The macrocyclization event described in Scheme 18 provides the natural stereochemical arrangement almost exclusively. You will note that both paths to cobyrinic acid (**4**) have now converged on a common intermediate. From bisnorcobyric acid abdeg pentamethylester c dimethylamide f nitrile (**75**), the journey to cobyrinic acid (**4**) was completed collaboratively by both groups.

8.3.9 Completion of the Woodward–Eschenmoser Total Synthesis of Cobyric Acid and Vitamin B₁₂

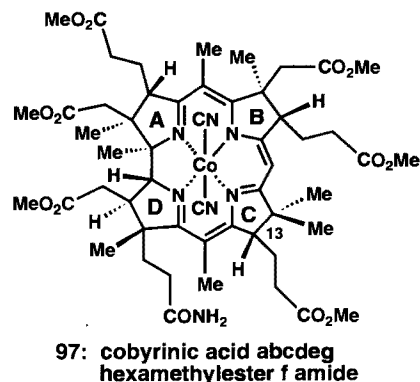
To complete the synthesis of cobyrinic acid (**4**) and therefore vitamin B₁₂ (**1**) from **75**, three significant challenges remain: two methyl groups, one at position 5 and the other at position 15, must somehow be introduced; the three-carbon side chain attached to position 17 in ring D must eventually terminate in a carboxyl group; and the remaining side chains must be made to terminate in primary amide groups. Scheme 20 presents the solution to the first of these three problems. By taking advantage of the nucleophilic character of an amide oxygen atom, intermediate **75** is readily transformed into lactone **94** on treatment with iodine and acetic acid, presumably through the intermediacy of a C-8 allylic iodide. At this juncture, it was anticipated that the fully substituted carbon atoms at positions 8 and 12 would shield position 10 from attack by alkylating agents. Treatment of **94** with chloromethyl benzyl ether in sulfolane at 75°C, followed by exposure to thiophenol, results in the completely selective incorporation of phenylthiomethyl groups at carbons 5 and 15; no attack on the hindered C-10 position is observed. It is thought that this reaction affords a bis(benzyloxymethyl) ether which is subsequently converted into a bis(chloromethylated) intermediate by hydrogen chloride. Displacement of both chloride substi-

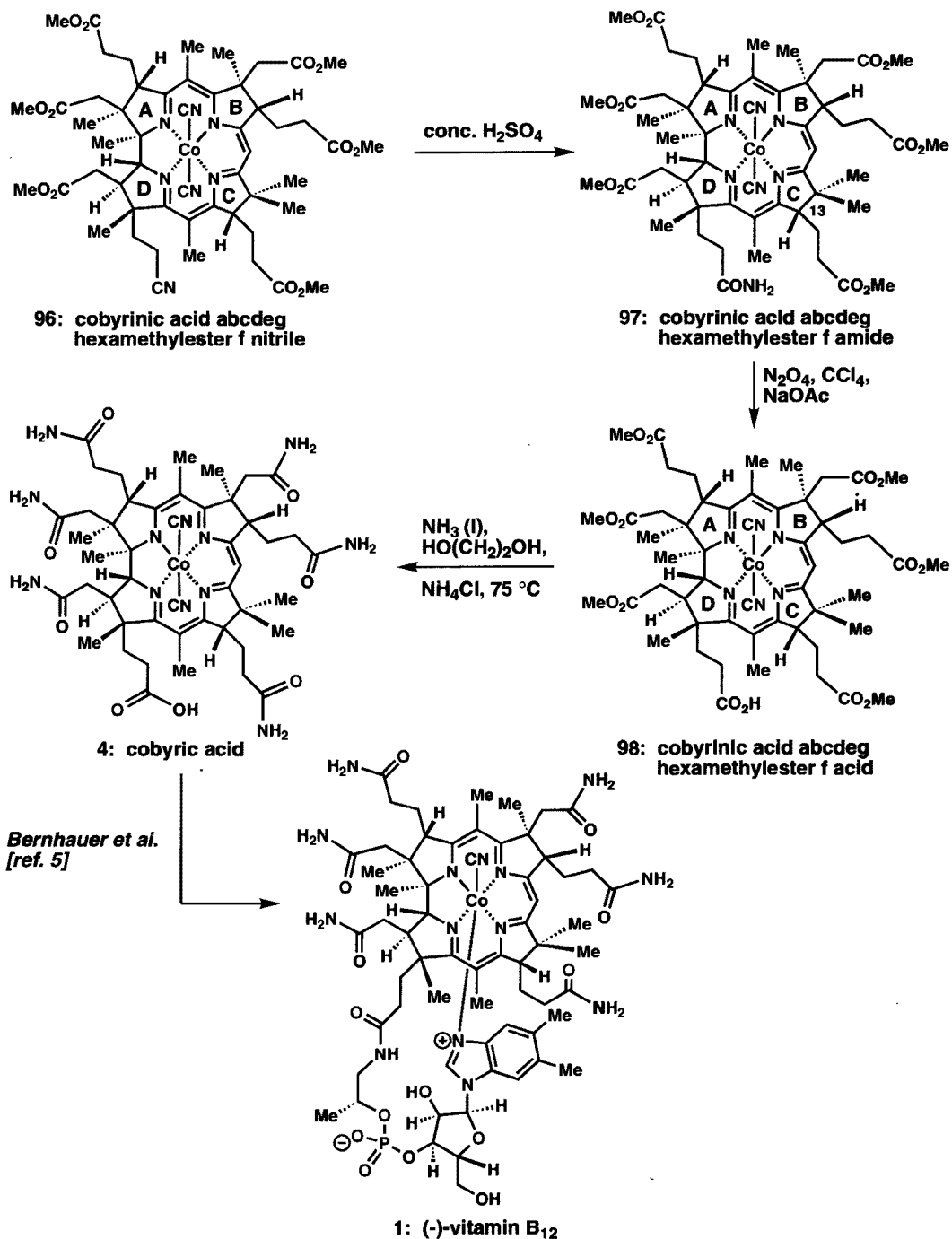


Scheme 20. Synthesis of cobyrinic acid abcddeg hexamethylester f nitrile **96**.

tuents by thiophenol then furnishes intermediate **95**. Reductive removal of both phenylthio groups with Raney nickel is accompanied by reduction of the lactone ring. Finally, esterification of the free carboxyl group with diazomethane affords cobyrinic acid abcddeg hexamethylester f nitrile (**96**). The task of introducing the requisite methyl groups at positions 5 and 15 has now been accomplished.

Scheme 21 presents the successful sequence of reactions that solved the remaining two problems and led to the completion of the synthesis of cobyrinic acid. Exposure of **96** to concentrated sulfuric acid for one hour brings about a clean conversion of the nitrile grouping to the corresponding primary amide grouping. The stability of the corrin nucleus under these rather severe conditions is noteworthy. This new substance, intermediate **97**, is identified as cobyrinic acid abcddeg hexamethylester f amide and it is produced along with a very similar substance which is epimeric to **97** at C-13. The action of sulfuric acid on **96** produces a diastereomeric



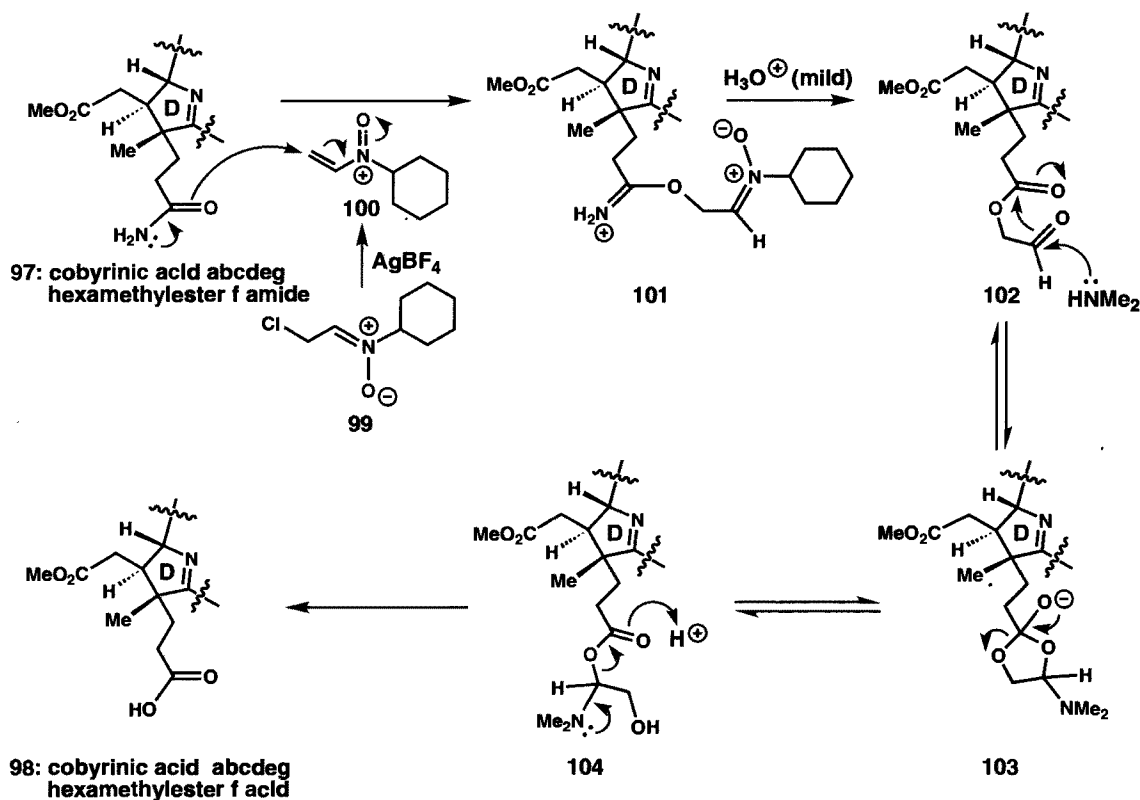
Scheme 21. Synthesis of (-)-vitamin B₁₂ (1).

mixture of primary amides in a ratio of 72:28 in favor of the undesired isomer. These stereoisomeric substances are, however, very readily separable by high-pressure liquid chromatography and it is possible to obtain the desired isomer (compound **97**) in pure form.

Two problems stand between intermediate **97** and the target cobyric acid (**4**). It is instructive at this point to closely examine the structure of **97**. Arranged around its periphery are six side chains which terminate in methoxycarbonyl groups and one side chain which terminates in a primary amide group. One problem requiring a solution is the selective hydrolysis of the primary amide grouping in this compound. At first glance, this problem may seem insurmountable by virtue of the fact that an amide is inherently less electrophilic and, therefore, less susceptible to attack by nucleophilic reagents than esters. Nevertheless, deaminations of amides using nitrous acid or some other nitrous derivative were well known, and both the Woodward and Eschenmoser camps were certainly mindful of these precedents. Although initial model experiments were uniformly unsuccessful, the Cambridge group eventually discovered that when a solution of **97** in carbon tetrachloride is treated with dinitrogen tetroxide, in the presence of sodium acetate, the primary amide can be smoothly deaminated to cobyric acid abcddeg hexamethylester f acid (**98**). This is one solution to the amide hydrolysis problem.

In Zürich, however, Eschenmoser and his group developed an alternative method that permits the selective hydrolysis of the primary amide function in **97** – a method that, in our opinion, is among the most brilliant in this synthesis. Scheme 22 presents the elegant series of transformations that constitute Eschenmoser's solution to the amide hydrolysis problem. For clarity, only the relevant portion of intermediate **97** is illustrated. In the Eschenmoser method, the cyclohexylnitrone **99** derived from chloroacetaldehyde is treated, in the presence of amide **97**, with silver tetrafluoroborate. This reaction produces the highly electrophilic species **100** which reacts rapidly and selectively with the oxygen atom of the primary amide to give **101**. Mild acid hydrolysis of both carbon–nitrogen double bonds then furnishes formyl ester **102**. The desired carboxylic acid **98** is produced in good yield when this formyl ester is treated with dimethylamine in isopropanol. Dimethylamine attacks the more electrophilic aldehyde carbonyl and then, after an equilibrium transfer of the acyl group, a situation is created that can result in an irreversible release of carboxylic acid **98** (see **104**→**98**). The six methoxycarbonyl groups are impervious to these conditions.

To complete the arduous journey to cobyric acid (**4**), all that remains is the conversion of all six ester groups in **98** into primary amide groups (Scheme 21). Although this functional group transformation is seemingly straightforward, it required a good deal of careful experimentation. When a solution of **98** in liquid ammonia and ethylene glycol is heated to 75 °C in the presence of a catalytic amount of ammonium chloride, cobyric acid (**4**) is obtained in



Scheme 22. Eschenmoser's method for amide hydrolysis.

nearly quantitative yield. You will recall that, in 1960, Bernhauer *et al.* demonstrated that cobyric acid (**4**) is readily transformed into vitamin B₁₂ (**1**).⁵ The formal total synthesis of vitamin B₁₂ (**1**) is now, therefore, complete.^{1,16}

8.4 Conclusion

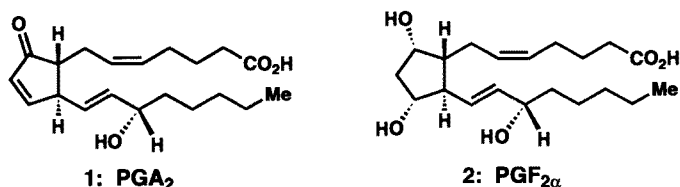
In this chapter, we have attempted to address one of the most significant achievements in organic chemistry. Indeed, the total synthesis of vitamin B₁₂, the culmination of 12 years of extensive research by two groups, has profoundly influenced the science of organic chemistry. Although we have presented the salient accomplishments recorded during the course of this remarkable synthesis, we strongly encourage students of organic synthesis to consult the original writings of Professors Woodward^{1a-c} and Eschenmoser^{1d,f,g,7d} for more detailed and certainly more pedagogical accounts.

From the perspective of the vitamin B₁₂ synthesis, it would be appropriate to contrast the traditional and contemporary roles of organic synthesis.^{1d} Before the advent of sophisticated physical methods, X-ray crystallography in particular, organic synthesis assumed the important role of confirming a constitutional hypothesis which originated from a degradative assault on a natural product. Indeed, during the classical period of natural products chemistry, an unambiguous synthesis played a decisive role in the elucidation of a natural product's structure. In addition, knowledge about the chemical properties of new structures was obtained, in many instances, as a result of chemical degradative studies. As physical methods matured, the importance of degradative work as a means of elucidating new structures faded. Contemporary natural products and synthetic organic chemists are the beneficiaries of powerful spectroscopic, crystallographic, and other physical methods. As impressive and necessary as these technological developments have been, we have had to pay a substantial price. By disposing of the archaic endeavor of chemical degradation, we have sacrificed an important source of information. Today, studies in natural product total synthesis most often commence with an established structure, but with an ignorance of its chemical properties. This fact confers much importance to synthetic work because it is through synthesis that we are able to achieve an intimate familiarity with the chemical properties of new molecules;^{1d} synthesis must shoulder the burden of acquiring the information that was once a fortuitous by-product of chemical degradation studies. Of course, even greater importance is conferred upon synthetic work in those cases where a new substance is not amenable to chemical degradation; vitamin B₁₂ is a conspicuous example. We contend that target-directed studies in organic synthesis are as important and perhaps even more so today than they have been in the past.¹⁷

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16. In March 1976, M.A. Wunola and R.B. Woodward accomplished the conversion of cobyrinic acid (**4**) to vitamin B₁₂ (**1**). The total synthesis of vitamin B₁₂ can thus be claimed, see: reference 1d, footnote 11, p. 1420. The formal total synthesis of **1** had been accomplished in 1973.
17. We are grateful to Prof. A. Eschenmoser for helpful comments on this chapter.



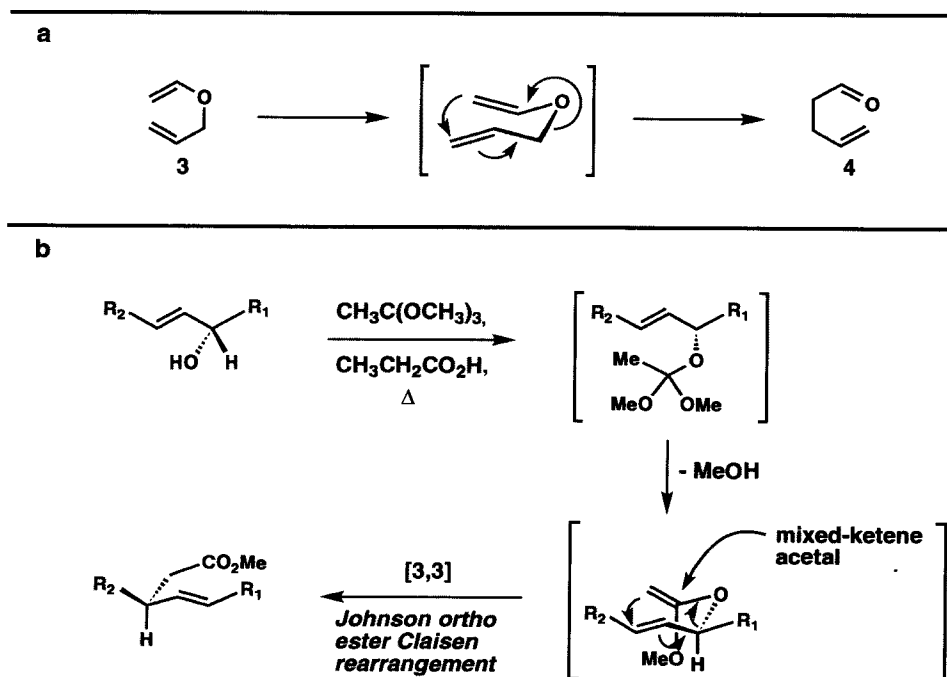
G. Stork (1976, 1978)

Prostaglandin A_2 (PGA_2) and Prostaglandin $F_{2\alpha}$ ($\text{PGF}_{2\alpha}$)

9.1 Introduction

The Claisen rearrangement and its many variants constitute a group of pericyclic reactions that is extremely valuable in organic synthesis.¹ In its most basic form, the Claisen rearrangement is the [3,3] sigmatropic rearrangement of allyl vinyl ether (**3**) to give 4-pentenal (**4**) (see Scheme 1a); it accomplishes the homologation of an allylic system through a process that creates a new carbon–carbon bond and, in substituted cases, it can create vicinal stereochemical relationships in an extremely efficient and controlled fashion by virtue of its highly organized transition state geometry. In this chapter, we address the total syntheses of PGA_2 (**1**) and $\text{PGF}_{2\alpha}$ (**2**) by Gilbert Stork and his group at Columbia.² These two syntheses exemplify the value of the Claisen rearrangement as a tool for the elaboration of multifunctional organic molecules.

The Stork group accomplished elegant enantiospecific syntheses of both of these natural prostaglandins from simple and readily available carbohydrates using strategies that take advantage of the powerful and predictable Claisen rearrangement. In each synthesis, a carbohydrate-derived secondary allylic alcohol is employed as a substrate for a Johnson ortho ester Claisen rearrangement³ (see Scheme 1b) which accomplishes a smooth 1,3-transfer of asymmetry with concomitant creation of a key carbon–carbon bond. The general features of the Stork synthesis of PGA_2 (**1**) are outlined below.

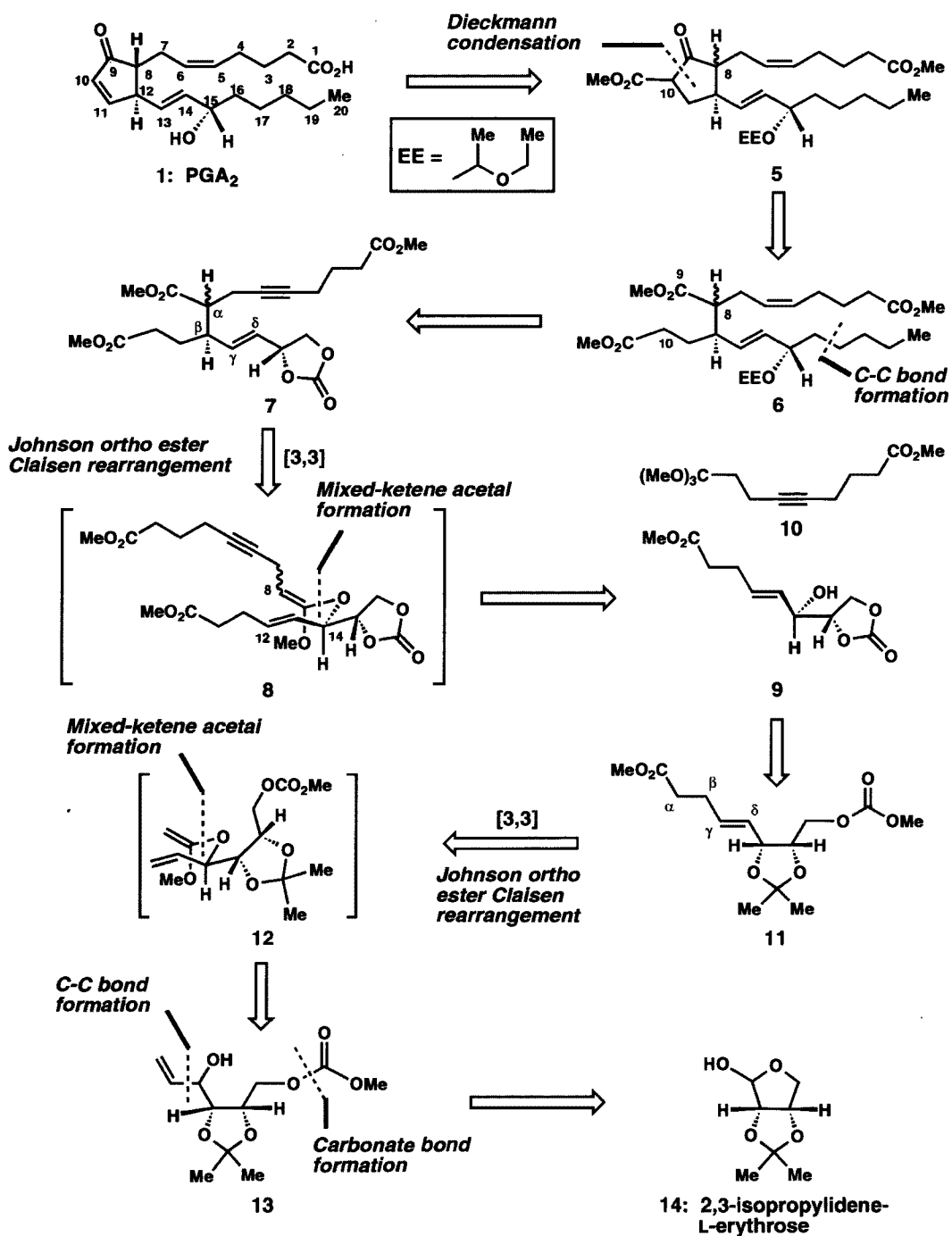


Scheme 1. Parent Claisen rearrangement (a) and the Johnson ortho ester variant (b).

9.2 Retrosynthetic Analysis and Strategy for PGA₂

Standard retrosynthetic manipulation of PGA₂ (**1**) converts it to **5** (see Scheme 2). A conspicuous feature of the five-membered ring of intermediate **5** is the β -keto ester moiety. Retrosynthetic cleavage of the indicated bond in **5** furnishes triester **6** as a potential precursor. Under basic conditions and in the synthetic direction, a Dieckmann condensation⁴ could accomplish the formation of a bond between carbon atoms 9 and 10 in **6** to give intermediate **5**. The action of sodium hydroxide on intermediate **5** could then accomplish saponification of both methyl esters, decarboxylation, and epimerization adjacent to the ketone carbonyl to establish the necessary, and thermodynamically most stable, *trans* relationship between the two unsaturated side-chain appendages.

Intermediate **7**, a viable precursor of intermediate **6**, possesses a γ,δ -unsaturated ester, the structural prerequisite, or retron, for the ortho ester Claisen transform.⁵ In the synthetic direction, the convergent union of intermediates **9** and **10** could give mixed-ketene acetal **8**; the intermediacy of **8** should be brief, for it should readily

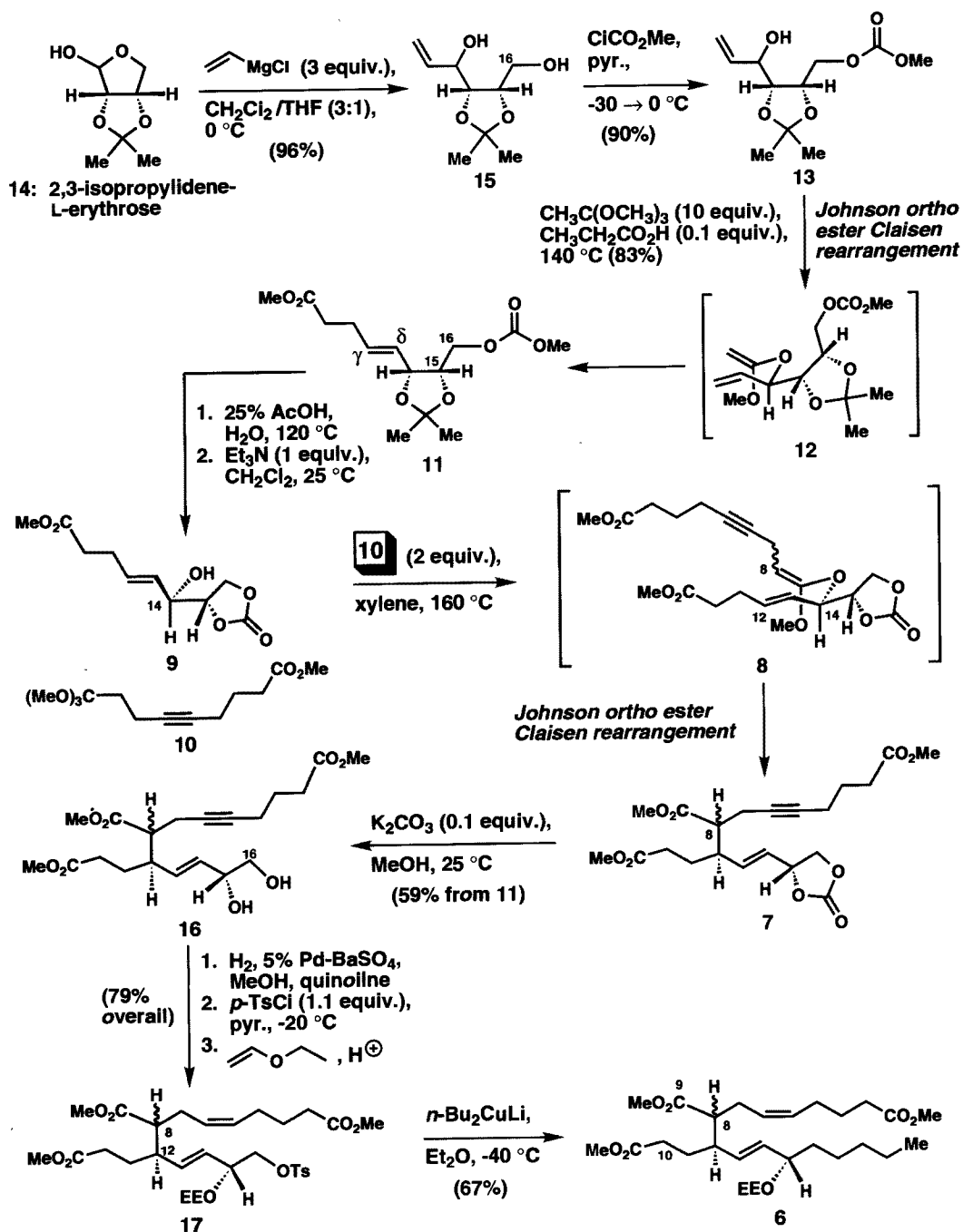
Scheme 2. Retrosynthetic analysis of PGA₂ (1).

participate in a Claisen rearrangement to give **7**. In acyclic systems, a hallmark of the Claisen rearrangement is its highly organized, chairlike, transition state geometry⁶ which, in this application, permits stereochemistry to be transferred across the allylic system from C-14 to C-12 (relative asymmetric induction). In intermediate **8**, the carbonate ring adopts the favored pseudoequatorial orientation and induces the Johnson-Claisen rearrangement to proceed across the indicated diastereoface of the allylic (C12–C13) double bond. The relative orientation of the two unsaturated appendages in **7** would stem directly from the geometries of the two olefins in **8** (internal asymmetric induction).⁷ It is interesting to note that even if **7** is produced as a stereoisomeric mixture, epimeric at C-8, it should be possible to correctly establish that stereocenter through epimerization after formation of the five-membered ring (see intermediate **5**).

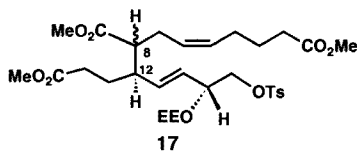
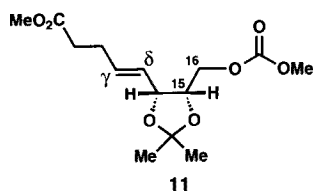
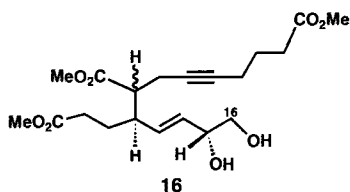
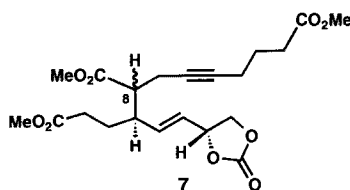
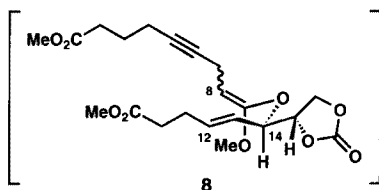
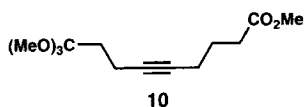
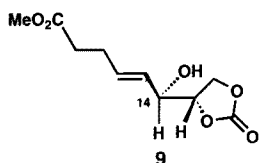
Intermediate **11**, the projected precursor of **9**, could be derived in one step from allylic alcohol **13** through a Johnson ortho ester Claisen rearrangement. In addition to its ability to create vicinal stereochemical relationships in a predictable fashion, the Claisen rearrangement provides a very reliable and powerful method for the construction of *trans* di- and even trisubstituted carbon–carbon double bonds from secondary allylic alcohols.^{3b} The *trans* double bond selectivity exhibited by the Claisen rearrangement is a natural consequence of its organized chairlike transition state conformation (for example, see intermediate **12**). Finally, **13** can easily be traced to a derivative of L-erythrose, compound **14**. Based on the above analysis, a strategy for the total synthesis of PGA₂ and PGF_{2α} was thus evolved.

9.3 Total Synthesis of PGA₂

The Stork synthesis of PGA₂^{2a} (see Scheme 3) commences with the reaction of 2,3-isopropylidene-L-erythrose (**14**) with three equivalents of vinyl magnesium chloride to give diol **15** in 96% yield. Allylic alcohol **13** is formed smoothly (90% yield) after selective protection of the primary hydroxyl group (C-16, PG numbering) as a methyl carbonate. In the presence of excess trimethyl orthoacetate and a catalytic amount of propionic acid, intermediate **13** is easily transformed into the γ,δ -unsaturated methyl ester **11** in a yield of 83% through a Johnson-Claisen rearrangement (see intermediate **12**). The selection of a methyl carbonate as a protecting group for the C-16 primary hydroxyl group is not arbitrary; it was reasoned that its proximity to the adjacent oxygen atom at C-15 could provide the basis for a very simple solution to a hydroxyl group differentiation problem. Hydrolysis of the acetonide ring in **11** affords a diol which is smoothly transformed into cyclic carbonate **9** on treatment with triethylamine. In this way, the C-14 allylic hydroxyl



Scheme 3. Synthesis of intermediate 6.

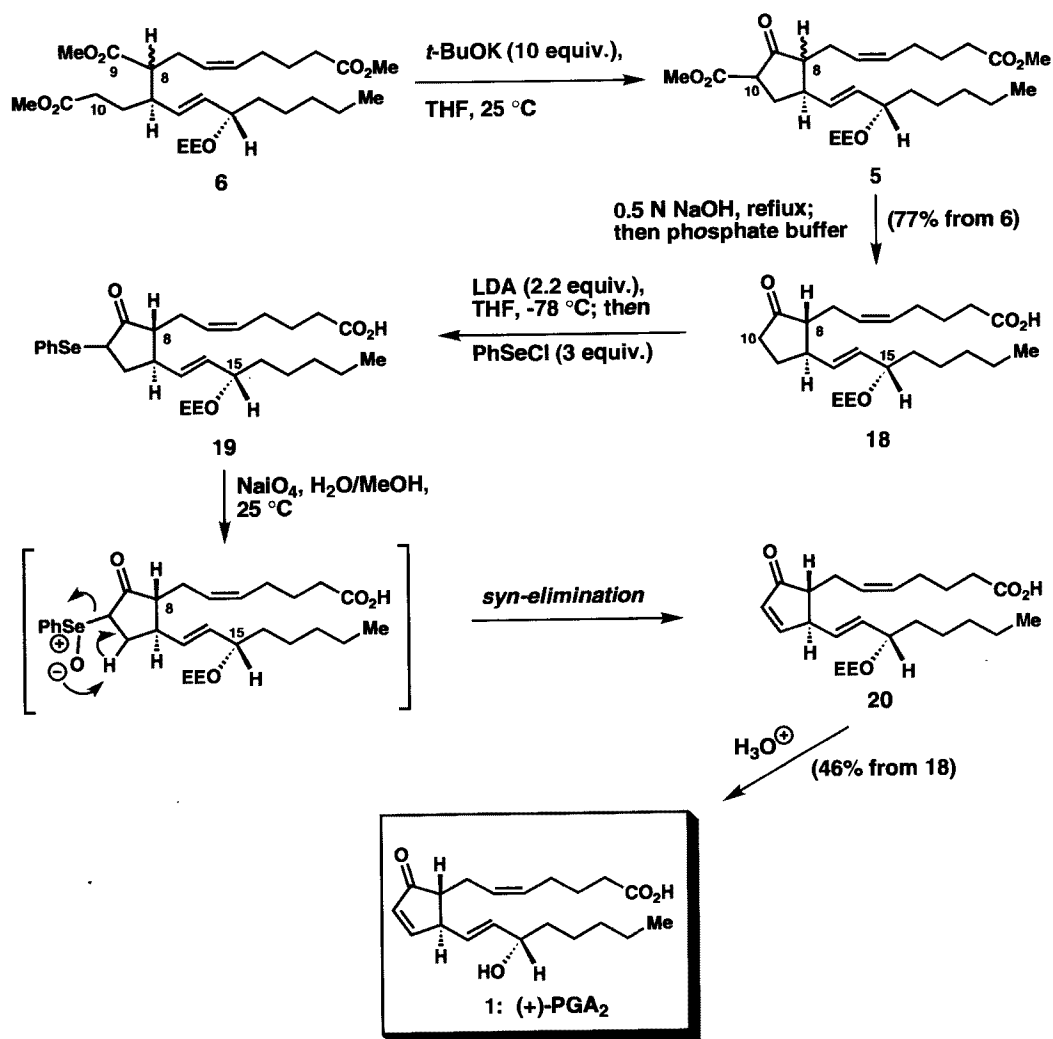


group can be selectively unveiled for the next Claisen rearrangement.

When a solution of allylic alcohol **9** and trimethyl ortho ester **10** in xylene is heated to 160 °C, a Johnson-Claisen rearrangement proceeds, through the intermediacy of mixed-ketene acetal **8**, to give intermediate **7** as a mixture of C-8 epimers. Although a number of interesting and effective protocols have been developed for the purpose of controlling the geometry of the vinyl ether portion of Claisen rearrangement substrates,¹ it is generally difficult to define ketene acetal stereochemistry using the Johnson variant. Nevertheless, it is important to keep in mind that the production of **7** as a mixture of C-8 epimers is ultimately of no consequence because this stereocenter can be defined at a later stage through a thermodynamically controlled epimerization. It is also interesting to note that although the stereogenic center at C-14 in **8** is sacrificed during the course of the [3,3] sigmatropic event, it nevertheless controls the emergence of new asymmetry at C-12, a process that Mislow has referred to as "self-immolative" asymmetric induction.⁸ After purification of **7** and solvolysis of the cyclic carbonate with basic methanol, diol **16** is formed in an overall yield of 59 % from **11**.

Among the tasks remaining is the replacement of the C-16 hydroxyl group in **16** with a saturated butyl side chain. A partial hydrogenation of the alkyne in **16** with 5 % Pd-BaSO₄ in the presence of quinoline, in methanol, followed sequentially by selective tosylation of the primary hydroxyl group and protection of the secondary hydroxyl group as an ethoxyethyl ether, affords intermediate **17** in 79 % overall yield from **16**. Key intermediate **6** is formed in 67 % yield upon treatment of **17** with lithium di-*n*-butylcuprate.

In the context of intermediate **6**, a Dieckmann condensation⁴ should proceed with reasonable facility by virtue of the close spatial relationship between the active methylene at C-10 and the electrophilic ester carbonyl at C-9. When intermediate **6** is subjected to the action of excess potassium *tert*-butoxide, the desired cyclization proceeds to give β -keto ester **5** as a mixture of stereoisomers (Scheme 4). Exposure of this mixture to 0.5 N sodium hydroxide at reflux accomplishes the conversion of **5** to **18** after acidification with phosphate buffer. In this highly productive step, both methyl esters are saponified with concomitant decarboxylation at C-10, and the side chain bearing stereocenter at C-8 is epimerized to the natural configuration. To complete the synthesis, it is necessary to introduce unsaturation into the cyclopentanone ring and unmask the hydroxyl group at C-15. Successive treatment of **18** with 2.2 equivalents of lithium diisopropylamide (LDA) and 3 equivalents of phenylselenenyl chloride provides α -phenylselenoketone **19**. The action of 2.2 equivalents of LDA on **18** produces a dianion which subsequently reacts with phenylselenenyl chloride at C-10. Oxidative *syn*-elimination of the phenylseleno substituent with NaIO₄, followed by hydrolytic removal of the ethoxyethyl protecting group in **20**, furnishes (\pm)-PGA₂ (**1**) in an overall yield of 46 % from **18**.

Scheme 4. Synthesis of $(\pm)\text{-PGA}_2$ (1).

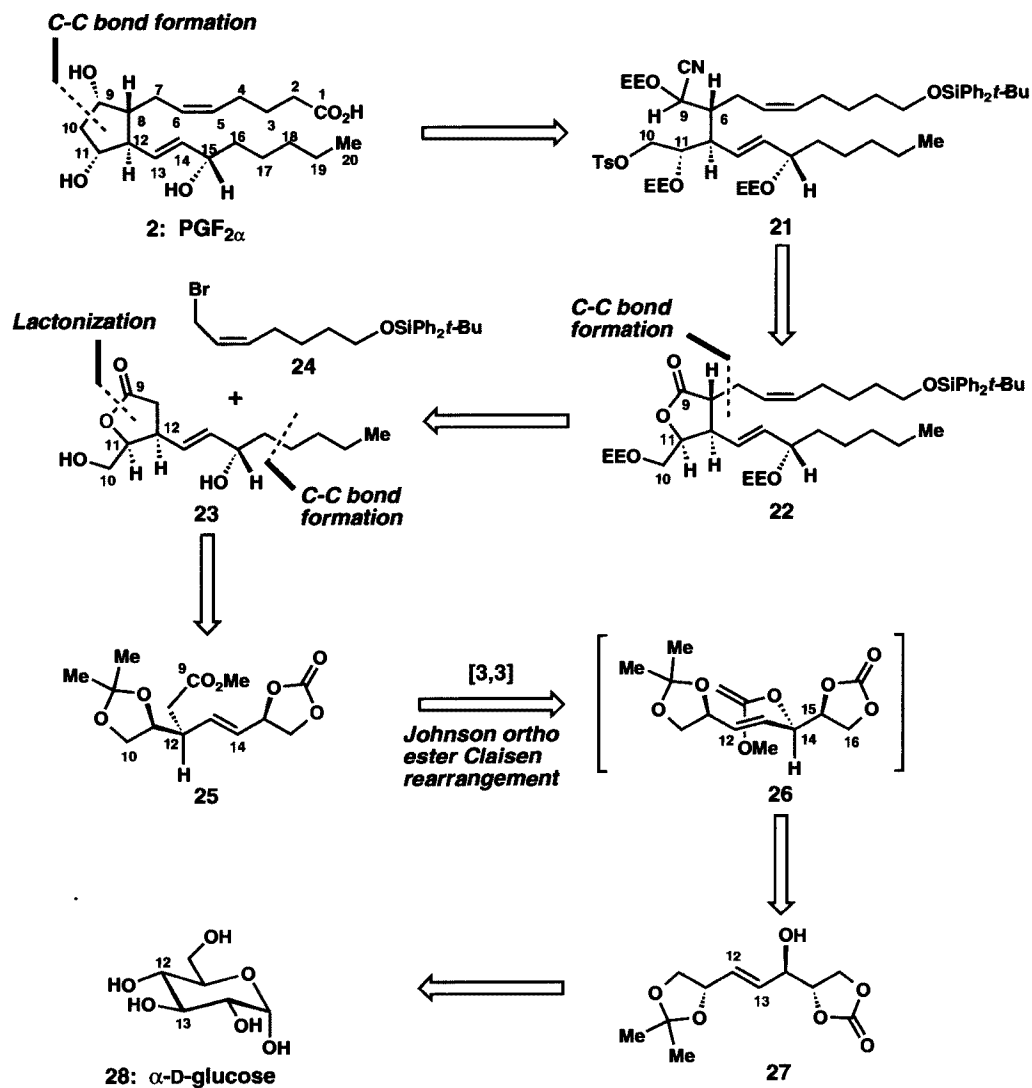
Two years after the disclosure of the total synthesis of PGA₂ from a carbohydrate derivative, the Stork group reported the enantiospecific assembly of PGF_{2α} from D-glucose.^{2b} In direct analogy to the PGA₂ synthesis,^{2a} the Stork group cleverly manipulated the asymmetry of a sugar and accomplished the stereospecific formation of a key carbon-carbon bond through a diastereoselective Johnson ortho ester Claisen rearrangement. The Stork synthesis of PGF_{2α} is outlined retrosynthetically in Scheme 5.

9.4 Retrosynthetic Analysis and Strategy for PGF_{2α}

The PGF_{2α} molecule is more complex, particularly with respect to stereochemistry, than its relative PGA₂. The saturated five-membered ring of PGF_{2α} is the host of four contiguous asymmetric carbon atoms, two of which accommodate the same unsaturated side-chain appendages as those found in PGA₂. Retrosynthetic scission of the C9-C10 bond in **2** (see Scheme 5) provides protected cyanohydrin **21** as a potential precursor and key synthetic intermediate. Protected cyanohydrins are versatile functional groups; in addition to their traditional role as a carbonyl protecting group, protected cyanohydrins can alter the reactivity profile of a molecule. For example, when a protected cyanohydrin is used to mask an aldehyde carbonyl, as it is in intermediate **21**, the electron-withdrawing cyano substituent imparts nucleophilic character to a carbon atom that was formerly electrophilic. When intermediate **21** is subjected to the action of a competent base, it should be possible to achieve deprotonation at C-9 to afford a resonance-stabilized carbanion or, to be more precise, an *acyl anion equivalent*.⁹ Thus, through the use of a protected cyanohydrin, a *reactivity umpolung*¹⁰ can be achieved.

In the context of **21**, it is instructive to note that a stabilized C-9 carbanion would find itself in proximity to a carbon atom bearing a suitable leaving group. Thus, it is conceivable that the action of base on **21** could induce an intramolecular S_N2-type reaction with concomitant formation of the requisite five-membered ring. To clarify the relationship between **21** and its projected precursor, intermediate **22**, it is instructive to recognize the correspondence between the oxygen atom at C-11 and C-9. The recognition that the cyclopentane ring of PGF_{2α} could originate from a substituted γ-lactone ring is an elegant feature of Stork's design.

Removal of the unsaturated side-chain appendage from C-8 in **22** provides diol lactone **23** and allylic bromide **24** as potential precursors. In the synthetic direction, a diastereoselective alkylation of a hydroxyl-protected lactone enolate derived from **23** with allylic bromide **24** could accomplish the assembly of **22**, an intermediate that possesses all of the carbon atoms of PGF_{2α}. It was anticipated that preexisting asymmetry in the lactone enolate would induce the



Scheme 5. Retrosynthetic analysis of PGF_{2α} (2).

alkylation to proceed across the less congested α face. Intermediate **25**, the retrosynthetic precursor of lactone **23**, possesses a γ,δ -unsaturated ester and could conceivably be elaborated in one step from allylic alcohol **27** through a diastereoselective Johnson ortho ester Claisen rearrangement via **26**. Allylic alcohol **27** is readily available in enantiomerically pure form from α -D-glucose (**28**).

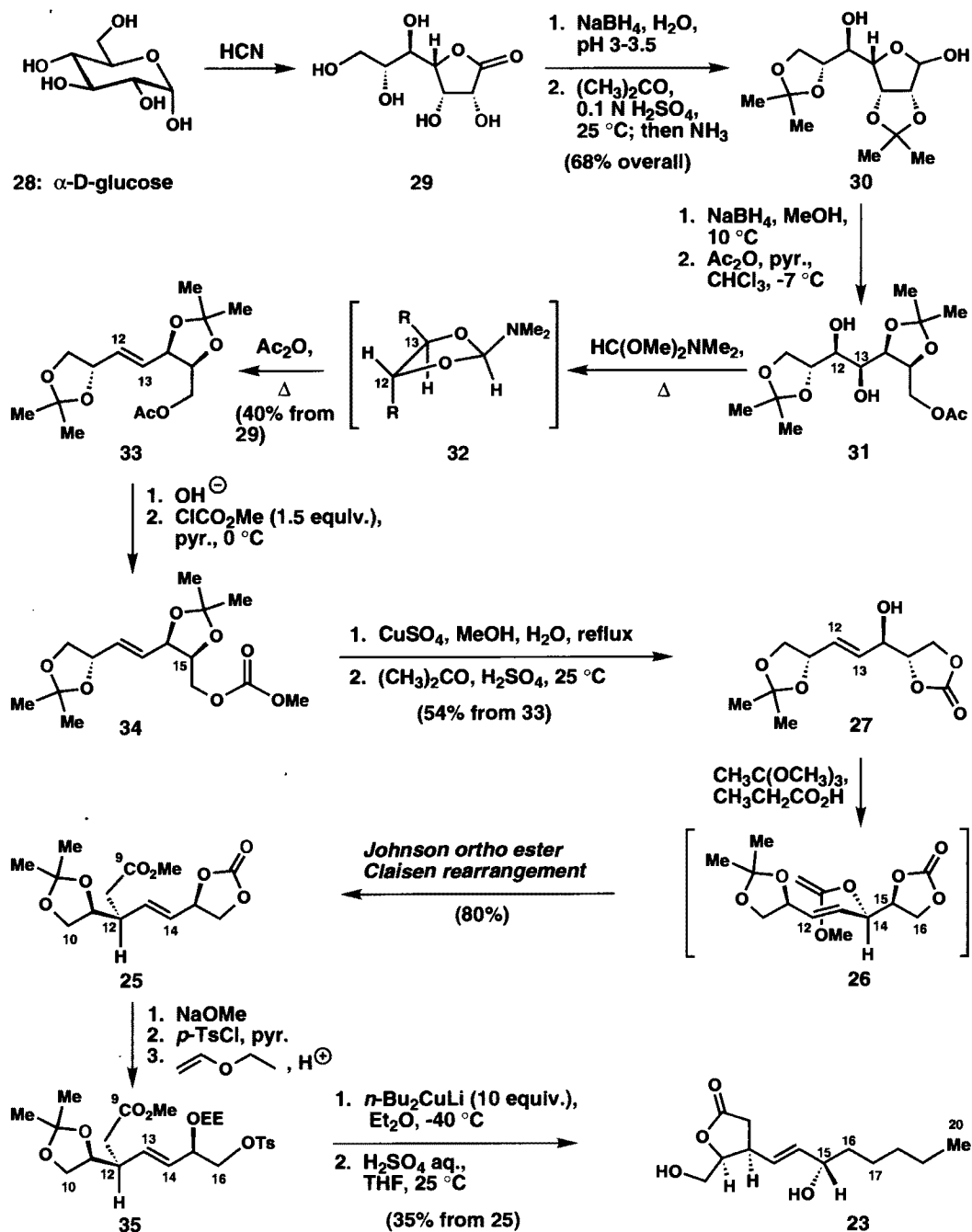
9.5 Total Synthesis of PGF_{2α}

The journey to PGF_{2α} from D-glucose (**28**) commences with the treatment of the latter substance with hydrogen cyanide to give the commercially available D-glycero-D-guloheptano-1,4-lactone (**29**) (see Scheme 6). Reduction of the lactone carbonyl to the corresponding lactol is easily achieved (~90 %) with sodium borohydride in an aqueous medium maintained at a pH of about 3–3.5. The reaction of this polyhydroxylated material with acetone in the presence of acid results in the simultaneous protection of four out of six hydroxyl groups, and provides the desired 2,3,6,7-diisopropylidene-D-glycero-D-guloheptose (**30**) in 75 % yield. Further reduction of lactol **30** with sodium borohydride, followed by selective acetylation of the resulting primary hydroxyl group, gives diol **31**.

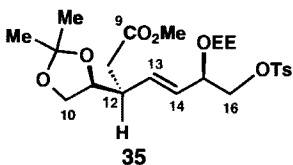
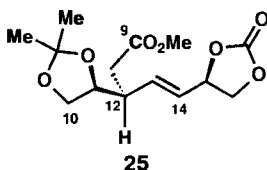
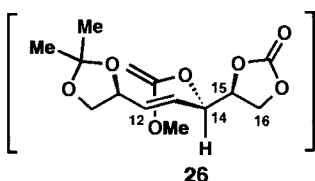
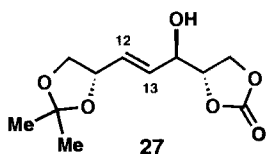
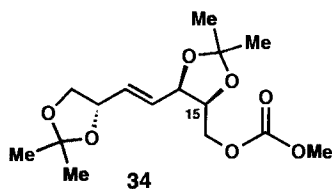
As we have seen in Scheme 5, a crucial transformation in the elaboration of PGF_{2α} from D-glucose is the diastereoselective and stereospecific Johnson-Claisen rearrangement of the mixed-ketene acetal **26** derived from allylic alcohol **27**. By virtue of the facility with which a similar Claisen rearrangement was performed during the course of Stork's PGA₂ synthesis, the prospects for the conversion of **27** into **25** seem excellent. As such is the case, it is intermediate **27** which constitutes the first synthetic objective. Obviously, at some stage during the course of the synthesis of intermediate **27**, unsaturation must be introduced between carbons 12 and 13 (PGF_{2α} numbering).

In 1970, it was disclosed that it is possible to achieve the conversion of dimethylformamide cyclic acetals, prepared in one step from vicinal diols, into alkenes through thermolysis in the presence of acetic anhydride.¹¹ In the context of **31**, this two-step process performs admirably and furnishes the desired *trans* alkene **33** in an overall yield of 40 % from **29**. In the event, when diol **31** is heated in the presence of *N,N*-dimethylformamide dimethyl acetal, cyclic dimethylformamide acetal **32** forms. When this substance is heated further in the presence of acetic anhydride, an elimination reaction takes place to give *trans* olefin **33**. Although the mechanism for the elimination step was not established, it was demonstrated in the original report that acetic acid, *N,N*-dimethylacetamide, and carbon dioxide are produced in addition to the alkene product.¹¹

The completion of the synthesis of intermediate **27** now only requires a few straightforward functional group manipulations.



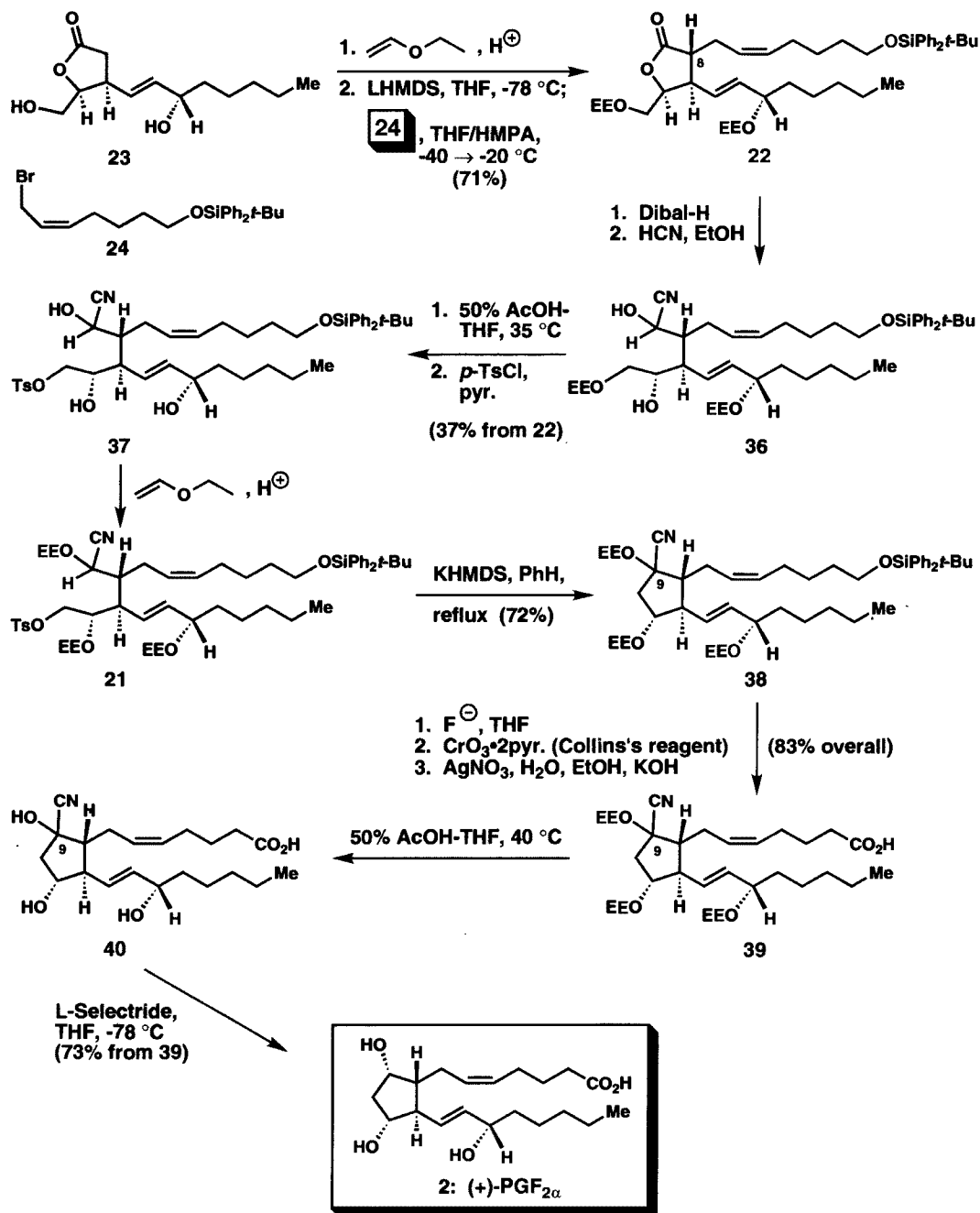
Scheme 6. Synthesis of intermediate 23.

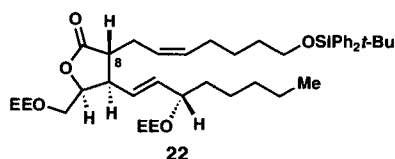


Saponification of the acetate, followed by conversion of the newly formed primary hydroxyl group to a mixed carbonate in the conventional way with methyl chloroformate and pyridine, provides intermediate **34**. At this juncture, it is instructive to draw attention to the fact that the oxygen atom at C-15 and the mixed carbonate in **34** occupy neighboring regions of space. Under conditions suitable for the removal of the isopropylidene groups in **34**, it seems unlikely that the liberated C-15 hydroxyl group would resist attacking the adjacent carbonate carbonyl to give, after expulsion of a molecule of methanol, a terminal five-membered cyclic carbonate. Indeed, exposure of **34** to cupric sulfate in refluxing aqueous methanol accomplishes the hydrolysis of both isopropylidene groups and the formation of a five-membered cyclic carbonate. After simultaneous protection of the vicinal hydroxyl groups, again in the form of an acetonide, intermediate **27** is obtained in an overall yield of 54% from **33**. In this manner, and as we have already witnessed in the synthesis of PGA₂, this straightforward sequence of functional group manipulations allows the secondary hydroxyl group at C-14 to be made selectively available for the crucial sigmatropic event.

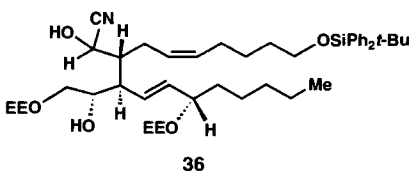
When intermediate **27** is treated with trimethyl orthoacetate and propionic acid, a Johnson ortho ester Claisen rearrangement takes place, through the intermediacy of mixed-ketene acetal **26**, to give intermediate **25**. This suprafacial sigmatropic event accomplishes a smooth C–O to C–C transfer of chirality and it is noteworthy that the newly formed stereogenic center at C-12 and the *trans* C13–C14 double bond are both expressed in the natural product. Cleavage of the cyclic carbonate in **25** with sodium methoxide, followed sequentially by selective tosylation of the primary hydroxyl group and protection of the C-15 secondary hydroxyl group, provides **35**, an intermediate that is properly functionalized for the introduction of the saturated four-carbon chain encompassing carbons 17–20. The selection of methoxide ion to cleave the cyclic carbonate in **25** is not arbitrary; although a host of other metal alkoxides would probably perform the task of cleaving the cyclic carbonate in **25** with the same facility that sodium methoxide does, it is also very probable that transesterification at C-9 would also occur to give a mixture of esters.

Replacement of the tosylate group in **35** with a saturated butyl chain is achieved with an excess of lithium di-*n*-butylcuprate and, after hydrolytic cleavage of the isopropylidene and ethoxyethyl (EE) protecting groups, lactone **23** is obtained in an overall yield of 35% from **25**. Acid-catalyzed hydrolysis of the isopropylidene furnishes a free hydroxyl group at C-11, which subsequently initiates lactonization by attacking the proximal methyl ester. After simultaneous protection of the two hydroxyl groups in **23** in the form of ethoxyethyl acetals (see Scheme 7), advantage is taken of the lability of the C–H bonds adjacent to the lactone carbonyl. In the presence of lithium bis(trimethylsilyl)amide (LHMDS), one of the two α -methylene hydrogens is removed as a proton to afford a lactone

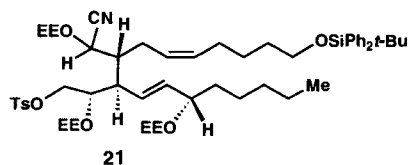
Scheme 7. Synthesis of (+)-PGF_{2α} (2).



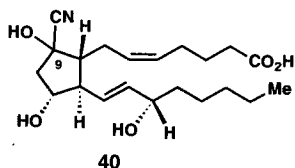
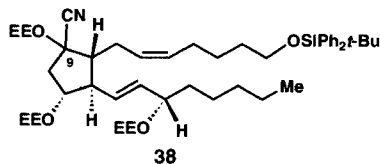
enolate which subsequently is alkylated with *cis* allylic bromide **24** to give exclusively intermediate **22**. Contained within **22** are all of the carbon atoms of PGF_{2α}, and it is noteworthy that the newly introduced unsaturated side-chain at C-8 is oriented correctly with respect to the molecular plane.



To create a setting that is favorable for the elaboration of the saturated five-membered ring, intermediate **22** is modified in the following way. Reduction of the γ -lactone carbonyl in **22** is achieved smoothly with diisobutylaluminum hydride (Dibal-H) to give an intermediate lactol which is then converted into cyanohydrin **36** with ethanolic hydrogen cyanide. A virtue of the cyanohydrin function is its stability to mild acids. It is thus possible to remove the two ethoxyethyl protecting groups with aqueous acetic acid in THF to give, after selective tosylation of the primary hydroxyl group, intermediate **37**. Intermediate **21** is obtained easily after protection of the remaining three hydroxyl groups in the form of ethoxyethyl acetals.



In 1971, the Stork group reported that aldehyde-derived protected cyanohydrins react smoothly with competent bases to give α -cyano-stabilized carbanions, or acyl anion equivalents, which can be alkylated with various alkyl halides to produce, in high yields, the protected cyanohydrin of a ketone.⁹ When the alkylating agent is tethered to the protected cyanohydrin, such a process could result in the formation of a carbocycle, and it is interesting to note that Stork and Takahashi had previously demonstrated that the five-membered ring of PGE₁ can be constructed in a very efficient manner through an intramolecular displacement of a tosylate by the carbanion derived from a protected cyanohydrin.¹² When intermediate **21** is subjected to the action of potassium bis(trimethylsilyl)amide (KHMDs) in refluxing benzene, cyclization proceeds to give intermediate **38** in a yield of 72%. After removal of the *tert*-butyldiphenylsilyl protecting group with fluoride ion, a Collins oxidation of the liberated primary hydroxyl group affords an aldehyde which is oxidized further with silver nitrate to give carboxylic acid **39** in an overall yield of 83% from **38**. The protected cyanohydrin at C-9 is completely stable under these conditions. Hydrolytic cleavage of the three ethoxyethyl protecting groups furnishes cyanohydrin **40**. In the context of **40**, the cyanohydrin function is particularly valuable because it masks a ketone that is rather unstable. Treatment of cyanohydrin **40** with lithium tri-*sec*-butylborohydride (L-Selectride) effects the conversion of the cyanohydrin functionality in **40** to a C-9 ketone, which is then reduced immediately under the reaction conditions to give, stereoselectively, (+)-PGF_{2α} (**2**) in a yield of 73% from **39**. Stork's elegant total synthesis of PGF_{2α} from D-glucose is now complete.



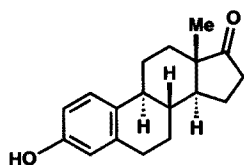
9.6 Conclusion

The elaboration of enantiomerically pure PGA_2 (**1**) and $\text{PGF}_{2\alpha}$ (**2**) from simple carbohydrate precursors by the Stork group exemplifies the value of the Claisen rearrangement for the synthesis of multifunctional organic molecules. In both syntheses, carbohydrate-derived secondary allylic alcohols are subjected to Johnson ortho ester Claisen rearrangements. The organized, chairlike transition state geometry for the sigmatropic event permits a smooth and predictable C–O to C–C transfer of asymmetry across the allylic system.

Stork's elegant use of a protected cyanohydrin function in the synthesis of $\text{PGF}_{2\alpha}$ (**2**) is also noteworthy. The electron-withdrawing cyano substituent in intermediate **21** (Scheme 7) confers nucleophilic potential to C-9 and permits the construction of the saturated cyclopentane nucleus of $\text{PGF}_{2\alpha}$ (**2**) through intramolecular alkylation. In addition, the C-9 cyanohydrin function contained within **40** is stable under the acidic conditions used to accomplish the conversion of **39** to **40** (see Scheme 7), and it thus provides suitable protection for an otherwise labile β -hydroxy ketone.

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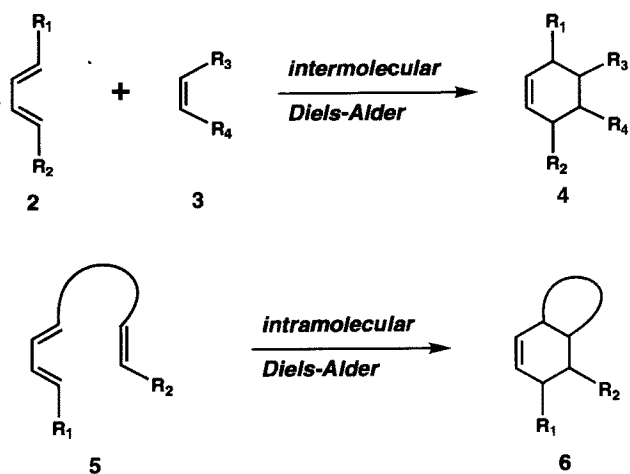
1: estrone

K. P. C. Vollhardt (1977)

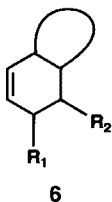
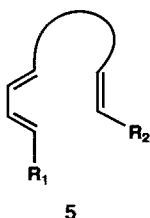
Estrone

10.1 Introduction

Reaction processes that can bring about significant increases in molecular complexity from simple building blocks occupy a special place in organic chemistry. In this regard, the venerable Diels–Alder reaction is noteworthy because it accomplishes the union of a 4π electron system with a 2π electron system, creating two new carbon–carbon bonds, a six-membered ring, and up to four contiguous stereocenters in one efficient step (see **2** + **3** → **4**, Scheme 1). The



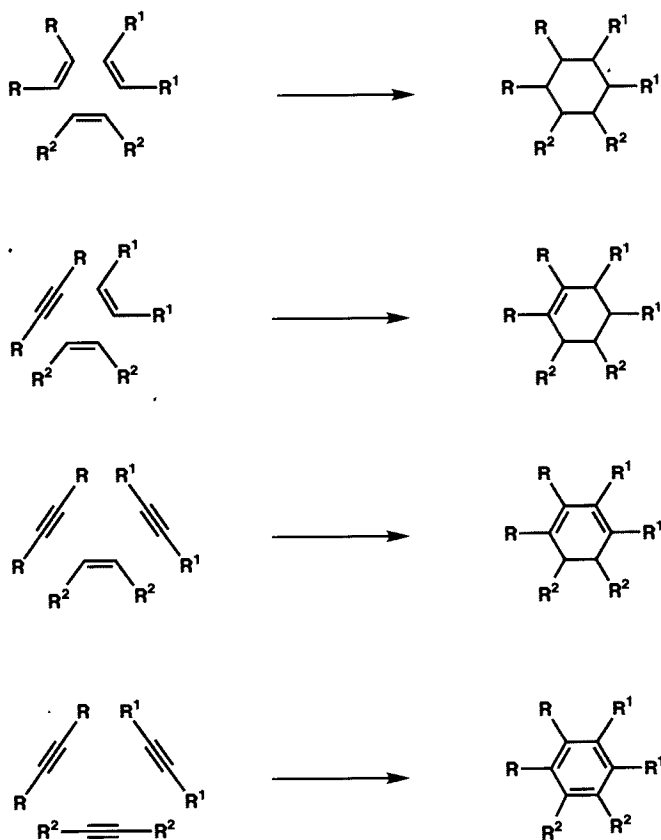
Scheme 1. Inter- and intramolecular Diels–Alder reactions.



impressive scope and utility of this intermolecular [4+2] cycloaddition process for the construction of stereochemically complex six-membered rings is well recognized.¹ It is interesting to note that an even more substantial structural change can be brought about simply by connecting the two unsaturated reaction partners (see **5** → **6**, Scheme 1). In **5**, the diene (4π e) and dienophilic (2π e) components are part of the same molecule. In such a setting, the probability that the two unsaturated moieties will react with each other can be enhanced, and the structural change that attends the intramolecular [4+2] cycloaddition event is impressive.² In a single operation, a rather complex bicyclic framework can be fashioned from a comparatively simple polyunsaturated acyclic molecule. The Diels–Alder cycloaddition is indeed a most productive process because it involves a simple summation of the reaction partners; all of the atoms that constitute the diene and dienophilic components are expressed in the [4+2] cycloadduct, none are wasted.³

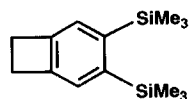
The Diels–Alder reaction accomplishes the formation of two carbon–carbon σ bonds at the expense of two carbon–carbon π bonds, and is among the most atom-economical³ and reliable carbon–carbon bond forming methods known in organic chemistry. Nonetheless, a potentially more powerful bond-forming strategy would be based on the [2+2+2] cycloaddition of three unsaturated entities (see Scheme 2).⁴ In these striking cyclotrimerizations, three new carbon–carbon bonds and a new carbocyclic ring with varying degrees of unsaturation would be produced in a single step. The efficiency of these general transformations is obvious. For example, the cyclotrimerization of three simple achiral alkenes could, in principle, furnish a saturated six-membered ring with six contiguous stereocenters! As in the case of the Diels–Alder reaction, these [2+2+2] cycloadditions would furnish products that are simply the sum of the starting materials.³

[2+2+2] Cycloaddition reactions would appear to hold great promise for the facile construction of carbocyclic systems. Nevertheless, examples of purely thermal [2+2+2] cycloadditions are rare. In 1866, Berthelot reported that benzene can be formed by the cyclotrimerization of acetylene at *ca.* 400 °C.⁵ Although thermal [2+2+2] cycloaddition reactions are symmetry-allowed and, in most cases, highly exothermic, it is likely that the significant decrease in entropy disfavors such transformations. On the other hand, [2+2+2] cycloadditions can be performed with much greater success by using transition metal complexes. In these transformations, the transition metal serves as a template upon which a variety of unsaturated molecules can undergo mutual bond formation. It was Reppe *et al.* who, in 1948, described the first transition metal mediated cyclooligomerization of acetylene.⁶ In this pioneering work, it was shown that nickel catalysts can induce the cyclooligomerization of acetylene to benzene, cyclooctatetraene, and styrene. It is now known that a large number of transition metal systems can promote [2+2+2] cycloadditions between alkynes, even functionalized alkynes, to give a variety of benzene derivatives.^{4b,7}

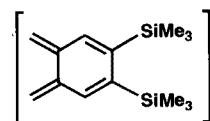


Scheme 2. Prototypical [2+2+2] cycloadditions.

Of the transition metal complexes capable of effecting the cyclotrimerization of alkynes to benzene derivatives, low-valent cobalt complexes such as the commercially available (η^5 -cyclopentadienyl)cobalt dicarbonyl, $\text{CpCo}(\text{CO})_2$, are among the most efficient.⁸ In 1975, Vollhardt *et al.* reported the important observation that a catalytic amount of $\text{CpCo}(\text{CO})_2$ can effect a cyclotrimerization reaction between 1,5-hexadiyne (**7**) and bis(trimethylsilyl)acetylene (BTMSA) (**8**) to give 4,5-bis(trimethylsilyl)benzocyclobutene **9** in >60% yield (see Scheme 3).⁹ In organic synthesis, benzocyclobutenes are very attractive substances because they undergo reversible opening of the four-membered ring on heating to give *ortho*-quinodimethanes (*ortho*-xylylenes) (see **10**, Scheme 3); the latter species are highly reactive and participate in facile [4+2] cycloaddition reactions with a wide variety of dienophiles.¹⁰ In fact, compound **11** can be produced in nearly quantitative yield from the reaction of **9** with maleic anhydride at 200 °C.

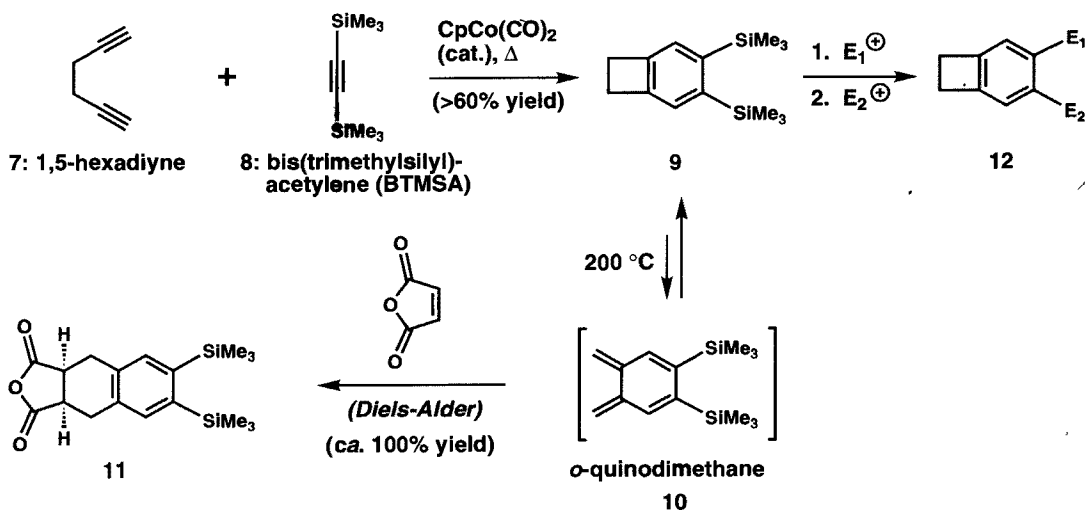


9



o-quinodimethane

10

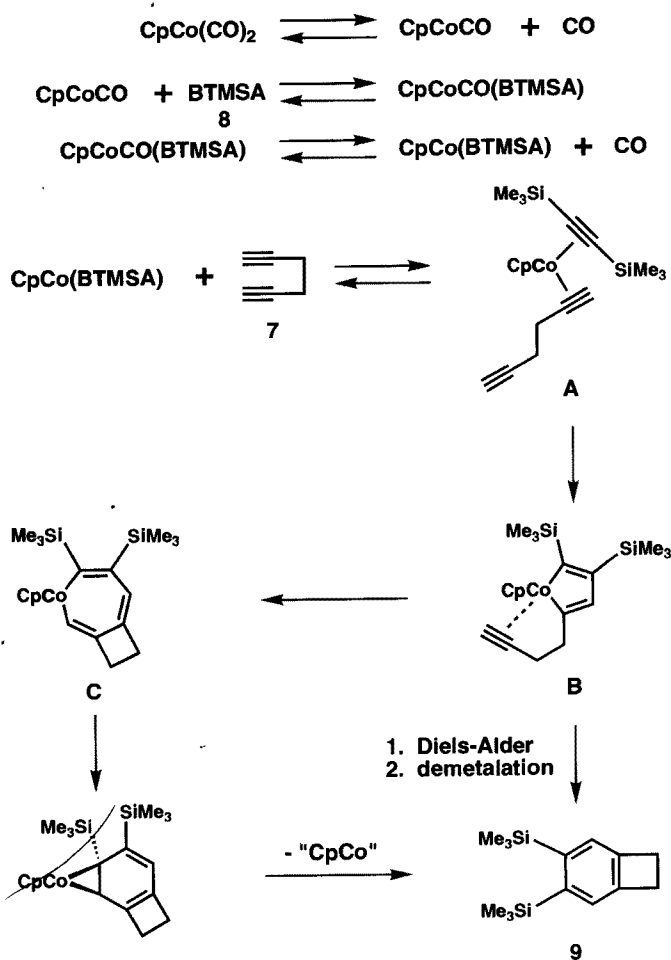


Scheme 3. CpCo(CO)_2 -catalyzed cyclotrimerization of 7 with 8, and subsequent reactions of benzo-cyclobutene 9.

The employment of BTMSA (8) in the cobalt-mediated cyclotrimerization described above is significant for three reasons. First, it was reasoned that the two trimethylsilyl substituents would confer sufficient steric bulk to 8 such that autocyclization (homooligomerization) would not occur. But in contrast to di-*tert*-butylacetylene, a compound too hindered either to autocyclize or to cyclotrimerize, BTMSA (8) might participate in cyclotrimerizations with α,ω -diynes because the carbon(sp)–silicon bond (*ca.* 1.9 Å) is longer than the carbon(sp)–carbon(sp³) bond (1.46 Å). As shown in Scheme 3, BTMSA (8) indeed undergoes cyclotrimerization with an α,ω -diyne in the presence of a catalytic amount of CpCo(CO)_2 . At least on the time scale of the cyclization experiment, BTMSA (8) does not react with itself. Second, because compound 8 is symmetrical, regiochemical problems would not arise in cyclotrimerizations with unsymmetrical α,ω -diynes. And third, the silylbenzene products that emerge from cyclotrimerizations of silylated alkynes are amenable to a variety of electrophilic aromatic substitution reactions.¹¹ For example, the two trimethylsilyl groups in benzocyclobutene 9 can be replaced by electrophiles, selectively and stepwise (see $9 \rightarrow 12$, Scheme 3).⁹ Interestingly, the rate associated with the replacement of the first trimethylsilyl group is *ca.* 40 times greater than that for the second. Differentially substituted benzene derivatives are thus readily available.

With respect to reaction mechanism, it is likely that CpCo(CO)_2 -mediated alkyne cyclotrimerizations proceed through discrete organometallic intermediates and are therefore not concerted.¹² A plausible mechanistic pathway for the CpCo(CO)_2 -catalyzed cyclotri-

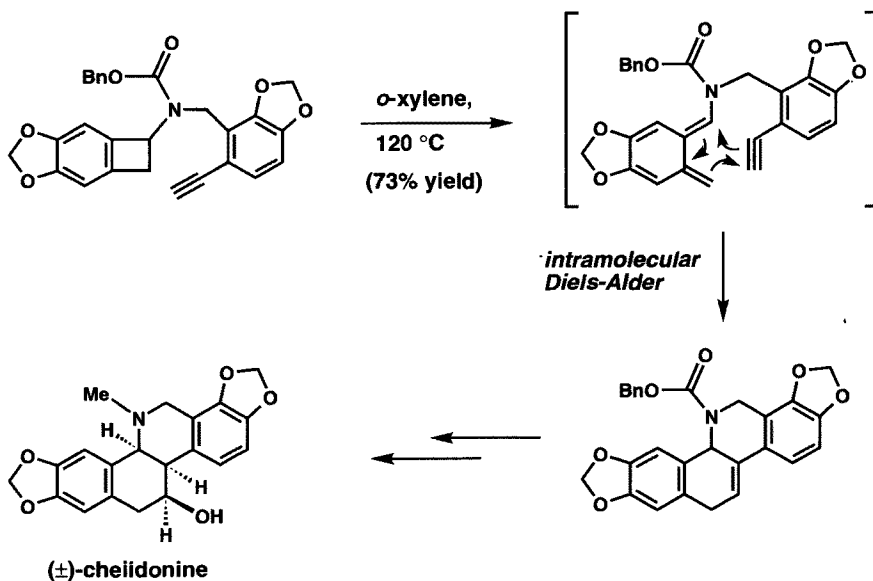
merization of BTMSA (**8**) with 1,5-hexadiyne (**7**) is presented in Scheme 4. After rate-determining dissociation of one molecule of carbon monoxide from $\text{CpCo}(\text{CO})_2$, the resulting coordinatively unsaturated cobalt complex $[\text{CpCoCO}]$ associates with an alkyne, probably BTMSA (**8**); it is likely that BTMSA functions as the first new ligand because BTMSA is used as the solvent in most of these reactions. At this point, the coordination site created upon dissociation of the remaining CO ligand can be occupied by one of the alkyne moieties of 1,5-hexadiyne to give the bisalkyne complex A. It is currently believed that the formation of complex A is followed by an oxidative coupling to give metallacyclopentadiene B. The conversion of A to B is described as an oxidation because the for-



Scheme 4. Presumed mechanism of the $\text{CpCo}(\text{CO})_2$ -catalyzed cocyclization of **7** with **8**.

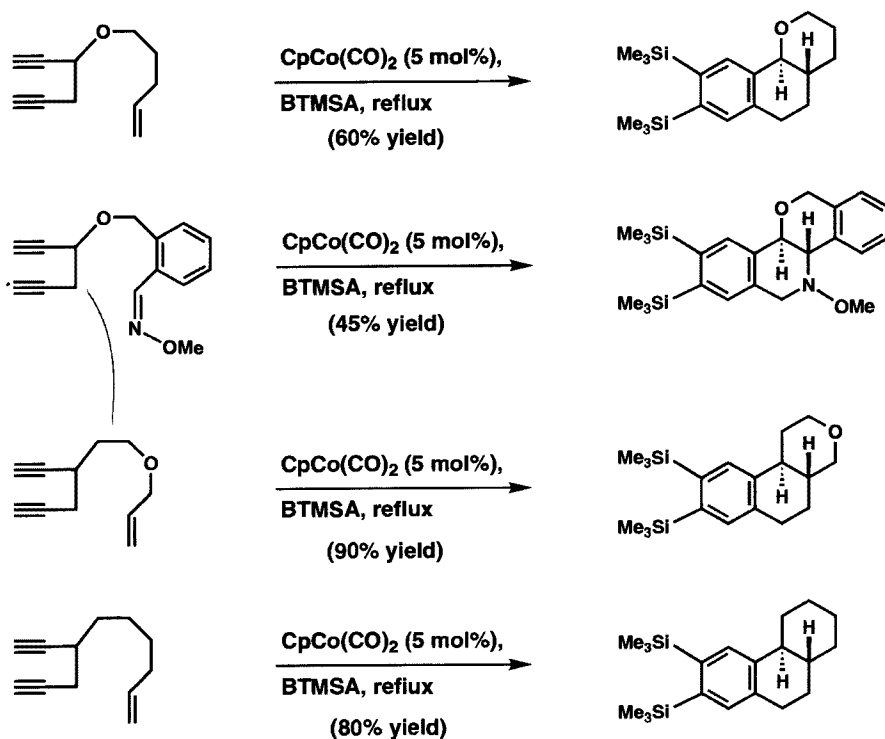
mal oxidation state of cobalt in B is two units higher than it is in A. Insertion of the remaining alkyne into the vinyl–cobalt bond would then give the metallacycloheptatriene C, after which ring contraction (reductive elimination) and extrusion of CpCo would furnish the final product. Alternatively, complex B could undergo conversion to the benzocyclobutene product through an intramolecular Diels–Alder reaction, followed by demetalation.

With a new method for the construction of benzocyclobutenes in hand, it was of interest to determine if a 1,5-hexadiyne substituted with a potential dienophile would take part in cobalt(1)-induced cyclotrimerization reactions. If so, then the initially formed benzocyclobutene product could, in principle, be converted *in situ* to a highly reactive *ortho*-quinodimethane through conrotatory ring opening and thence to a polycyclic ring system via an intramolecular Diels–Alder reaction. Indeed, intramolecular cycloadditions to reactive *ortho*-quinodimethanes are powerful and elegant transformations that can expedite the synthesis of a myriad of complex polycyclic systems. Wolfgang Oppolzer stands foremost among the developers of this efficient strategy for polycycle construction. Oppolzer was the first to demonstrate that reactive *ortho*-quinodimethanes, generated by thermally-induced opening of the four-membered ring of benzocyclobutenes, serve admirably as dienes in intramolecular [4+2] cycloaddition reactions with pendant dienophiles.¹³ This important work laid the foundation for an elegant synthesis of (±)-chelidone (see Scheme 5).^{13c} Not surprisingly, the efficiency of this methodology soon captured the attention of



Scheme 5. Oppolzer's synthesis of (±)-chelidone.

numerous groups; impressive achievements in the arena of natural products total synthesis soon followed, and these successes have been documented in several excellent reviews.¹⁰ But in spite of these achievements, the paucity of simple and effective methods for the synthesis of functionalized benzocyclobutenes has diminished the scope of this otherwise very attractive strategy for polycycle construction. The efficient cobalt-mediated alkyne cyclotrimerization methodology developed by Vollhardt *et al.* and the results summarized in Scheme 6 are thus particularly noteworthy. To bring about these productive transformations, a readily accessible 1,5-hexadiyne is simply added slowly to a refluxing solution of $\text{CpCo}(\text{CO})_2$ (5 mol %) in neat BTMSA.¹⁴ The resulting benzocyclobutene cyclotrimerization products are then converted *in situ* to the indicated polycyclic compounds via the intermediacy of *ortho*-quinodimethanes. These elegant tandem transformations¹⁵ accomplish the formation of five new carbon–carbon or carbon–nitrogen bonds and two contiguous stereocenters, and require only a catalytic amount of the cobalt(I) catalyst.

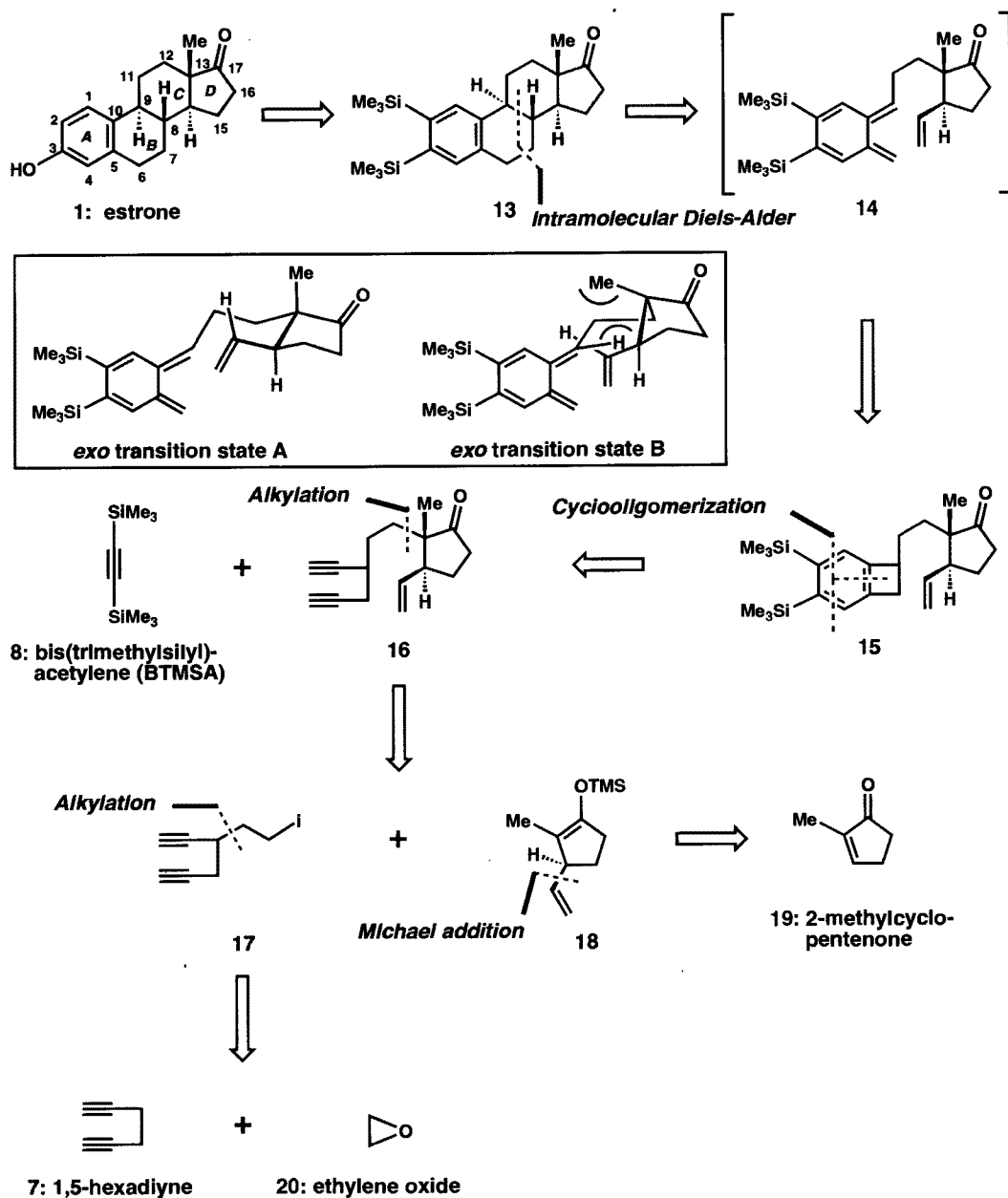


Scheme 6. Vollhardt's tandem alkyne cyclotrimerization/*o*-quinodimethane cycloaddition strategy for polycycle synthesis.

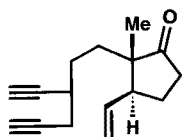
The homology of the tricyclic products in Scheme 6 to the ABC-ring portion of the steroid nucleus is obvious. In fact, the facility with which these tricyclic materials can be constructed from simple building blocks provided the impetus for the development of an exceedingly efficient synthesis of the female sex hormone, estrone (**1**). This important biomolecule has stimulated the development of numerous synthetic strategies and these have been amply reviewed.¹⁶ The remainder of this chapter is devoted to the brilliant synthesis of racemic estrone by K. P. C. Vollhardt *et al.*^{12,17}

10.2 Retrosynthetic Analysis and Strategy

The tetracyclic steroidal framework of the estrone molecule comprises four contiguous stereocenters and is distinguished by *trans-anti-trans* ring fusion stereochemistry. Compound **13** could serve as a retrosynthetic precursor for the natural product provided, of course, that the former compound can be manipulated in a regioselective manner (Scheme 7). Although direct precedent for the regioselective conversion of bis(trimethylsilyl)estratrienone **13** to estrone was not available, it was known that arylsilanes can be substituted with a variety of electrophiles.¹¹ Compound **13** presented itself as a very attractive synthetic intermediate because it could, in principle, be assembled in one pot from compounds **16** and **8**. In the synthetic direction and on the basis of the results summarized in Schemes 3 and 6, it was anticipated that cobalt-catalyzed cyclooligomerization of 1,5-diyne **16** and BTMSA (**8**) would furnish benzocyclobutene **15**. On heating, the strained benzocyclobutene **15** would be expected to participate in a conrotatory electrocyclic ring-opening reaction to give the highly reactive *ortho*-quinodimethane (*ortho*-xylylene) **14** as a transient intermediate. Although **14** could undergo electrocyclic ring closure back to benzocyclobutene **15**, it could also participate in a very productive intramolecular Diels–Alder reaction to give tetracycle **13**. Driven thermodynamically by the restoration of aromaticity, the intramolecular [4+2] cycloaddition event would accomplish the formation of two carbon–carbon σ bonds and rings B and C of the natural product. This particular strategy for the construction of estrone’s polycyclic framework was guided by the assumption that the crucial intramolecular Diels–Alder reaction would proceed through an *exo* transition state geometry. Of the two possibilities, *exo* transition state A, in which the vinyl grouping engages the β face of the *ortho*-quinodimethane, was deemed more favorable than B on steric grounds; molecular models show that *exo* transition state A closely resembles the energetically more favorable chair conformation, while *exo* transition state B adopts a boatlike conformation and is destabilized by non-bonding interactions. You will note that intramolecular [4+2] cycloaddition through *exo* transition state A would furnish tetra-



Scheme 7. Retrosynthetic analysis of estrone (1).



16

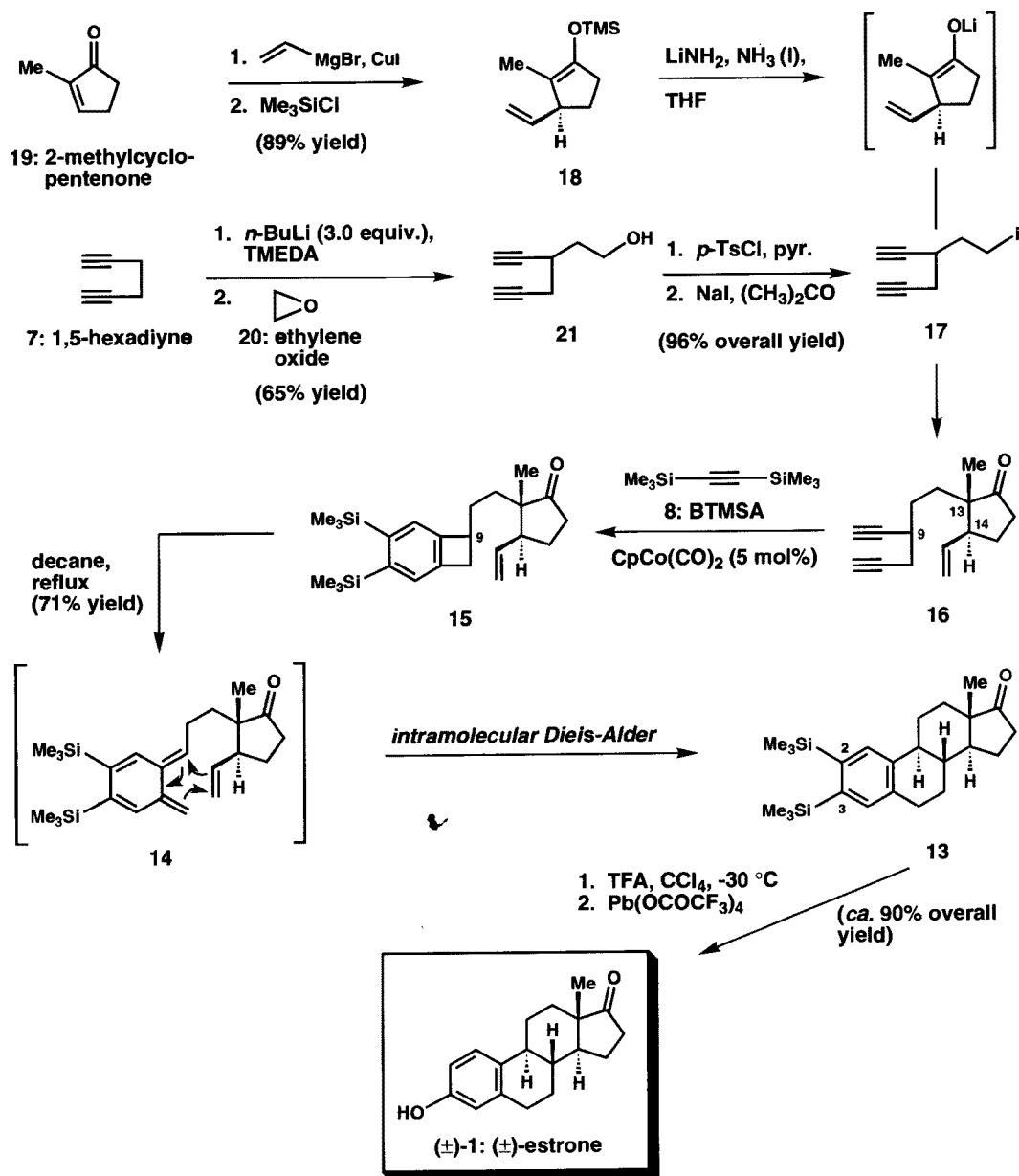
cycle **13** with the requisite *trans-anti-trans* ring fusion stereochemistry. Thus, through cobalt-catalyzed cyclotrimerization and intramolecular Diels–Alder reactions, monocycle **16** could conceivably be converted to tetracycle **13** without the isolation of any intermediates; if successful, this elegant consecutive reaction process^{15a} would accomplish the formation of five carbon–carbon bonds and two contiguous stereocenters!

The synthetic problem is now reduced to cyclopentanone **16**. This substance possesses two stereocenters, one of which is quaternary, and its constitution permits a productive retrosynthetic maneuver. Retrosynthetic disassembly of **16** by cleavage of the indicated bond furnishes compounds **17** and **18** as potential precursors. In the synthetic direction, a diastereoselective alkylation of the thermodynamic (more substituted) enolate derived from **18** with alkyl iodide **17** could afford intermediate **16**. While trimethylsilyl enol ether **18** could arise through silylation of the enolate oxygen produced by a Michael addition of a divinyl cuprate reagent to 2-methylcyclopentenone (**19**), iodide **17** can be traced to the simple and readily available building blocks **7** and **20**. The application of this basic plan to a synthesis of racemic estrone [(±)-**1**] is described below.

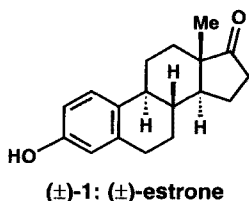
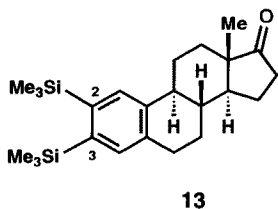
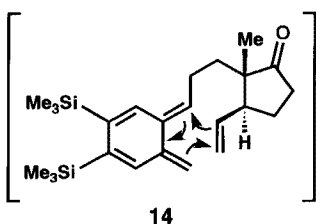
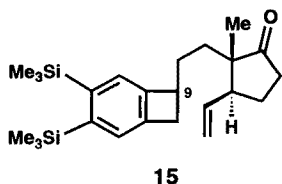
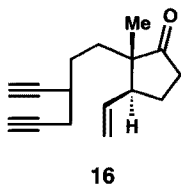
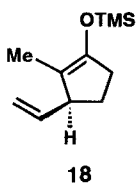
10.3 Total Synthesis

The efficient synthesis of estrone by Vollhardt and coworkers commences with the conjugate or Michael addition of the divinyl cuprate reagent derived from vinylmagnesium bromide (two equivalents) and CuI (one equivalent) to 2-methylcyclopentenone (**19**) (see Scheme 8). Trimethylsilylation of the resulting enolate oxygen then gives silyl enol ether **18** in 89% yield. In a parallel sequence of reactions, exposure of 1,5-hexadiyne (**7**) to three equivalents of *n*-butyllithium and one equivalent of tetramethylethylenediamine (TMEDA) results in the formation of a trilithiated compound. In the presence of ethylene oxide (**20**), a completely regioselective alkylation of the more nucleophilic propargylic position occurs to give the desired 3-substituted diynol **21** in 65% yield. Quantitative conversion of **21** to the corresponding *para*-toluenesulfonate ester, followed by a simple Finkelstein exchange, then provides iodide **17** in 96% overall yield.

An important stage in the synthesis has been reached. It was anticipated that cleavage of the trimethylsilyl enol ether in **18** using the procedure of Binkley and Heathcock¹⁸ would regiospecifically furnish the thermodynamic (more substituted) cyclopentanone enolate, a nucleophilic species that could then be alkylated with iodo-diyne **17**. To secure what is to become the *trans* CD ring junction of the steroid nucleus, the diastereoisomer in which the vinyl and methyl substituents have a *cis* relationship must be formed. In the



Scheme 8. Synthesis of (±)-estrone [(±)-1].



event, exposure of trimethylsilyl enol ether **18** to the action of lithium amide in liquid NH_3 -THF furnishes the corresponding enolate. When the latter is then treated with iodide **17**, an enolate alkylation reaction takes place to give a 2:1 mixture of *trans* (**16**) and *cis* diastereomers, each as a mixture of C-9 (steroid numbering) epimers (64 % total yield). Although the diastereoselectivity exhibited in this step is disappointing, the major product **16** (as a mixture of C-9 epimers) possesses the requisite C13-C14 relative stereo-relationship and can be separated chromatographically from the undesired *cis* stereoisomers. It should be noted that although the enolate produced in the initial conjugate addition step could, in principle, be alkylated directly with iododiyne **17**, it was found that the copper salts present in the reaction mixture interfered with the unprotected alkyne functions. Trimethylsilyl enol ether **18** is an attractive precursor for the requisite enolate because it can be easily purified by distillation.

We are now in a position to address the crucial and exciting cobalt-catalyzed cyclotrimerization of **16** with BTMSA (**8**). From the outset, the configuration at the benzylic position (C-9) in **15** was of no concern because both benzocyclobutene diastereomers should undergo conversion to the same *ortho*-quinodimethane **14** by a conrotatory opening of the four-membered ring. Gratifyingly, cocyclization of diyne **16** with BTMSA (**8**) in the presence of $\text{CpCo}(\text{CO})_2$ (5 mol %) under oxygen-free conditions furnishes a single estratrienone **13** in 18 % yield and a mixture of epimeric benzocyclobutenes **15** (56 % yield). When a solution of the stereoisomeric benzocyclobutenes in decane is heated to reflux, the desired ring opening and intramolecular Diels-Alder reactions take place smoothly, providing the desired estratrienone **13** in 95 % yield; the total yield of **13** is thus raised to 71 %. The diastereoselectivity of the conversion of **16** to **13** is truly remarkable, indicating that the crucial intramolecular Diels-Alder step proceeds preferentially through *exo* transition state A (Scheme 7).

The journey to estrone (**1**) is almost complete. In the event that a regioselective oxidative aryl-silicon bond cleavage could be achieved, 2,3-bis(trimethylsilyl)estratrienone **13** could serve as a potential precursor to estrone. Somehow, the trimethylsilyl group attached to C-3 has to be replaced by a hydroxyl group, while the C-2 trimethylsilyl group has to be replaced by a hydrogen atom. During the course of the synthesis, interesting and very useful observations suggested that the 2-position of 2,3-bis(trimethyl)silylated A-ring aromatic steroids is actually more susceptible to an electrophilic attack than the 3-position.^{17c} The increased reactivity of the 2-position in **13** can, in fact, be exploited to achieve the total synthesis of the estrone molecule. Under carefully controlled conditions, exposure of 2,3-bis(trimethylsilyl)estratrienone **13** to the action of trifluoroacetic acid (TFA) in CCl_4 at -30°C results in the formation of a 9:1 mixture of regioisomeric monotrimethylsilylated compounds in favor of the desired C-3 silylated steroid (90 % yield). A regioselective protodesilylation of **13** was thus achieved.

Finally, oxidative cleavage of the remaining aryl–silicon bond with lead tetrakis(trifluoroacetate), $[\text{Pb}(\text{OCOCF}_3)_4]^{19}$, furnishes (\pm)-estrone [(\pm)-**1**] in nearly quantitative yield.

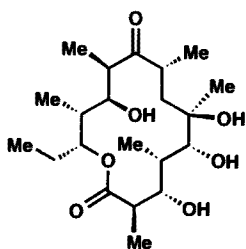
10.4 Conclusion

The total synthesis of (\pm)-estrone [(\pm)-**1**] by Vollhardt *et al.* is a novel extension of transition metal mediated alkyne cyclotrimerization technology. This remarkable total synthesis is achieved in only five steps from 2-methylcyclopentenone (**19**) in an overall yield of 22%. The most striking maneuver in this synthesis is, of course, the construction of tetracycle **13** from the comparatively simple diyne **16** by combining cobalt-mediated and *ortho*-quinodimethane cycloaddition reactions. This achievement bodes well for future applications of this chemistry to the total synthesis of other natural products.

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1: erythronolide B

E. J. Corey (1978)

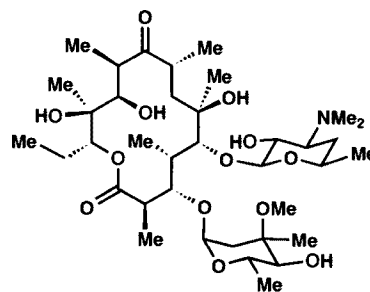
Erythronolide B

11.1 Introduction

The fungus *Streptomyces erythreus* is the source of a number of structurally related macrolide antibiotics that are collectively known as the erythromycins. The erythromycins occupy a prominent position in medicine by virtue of their useful antibacterial properties. Their use in therapy over the course of the last three decades has been widespread, and has resulted in the saving of many human lives. In this chapter, we address the landmark total synthesis of erythronolide B (**1**), the biosynthetic precursor of all the erythromycins, by E.J. Corey and his coworkers which was carried out at Harvard in the 1970s.¹

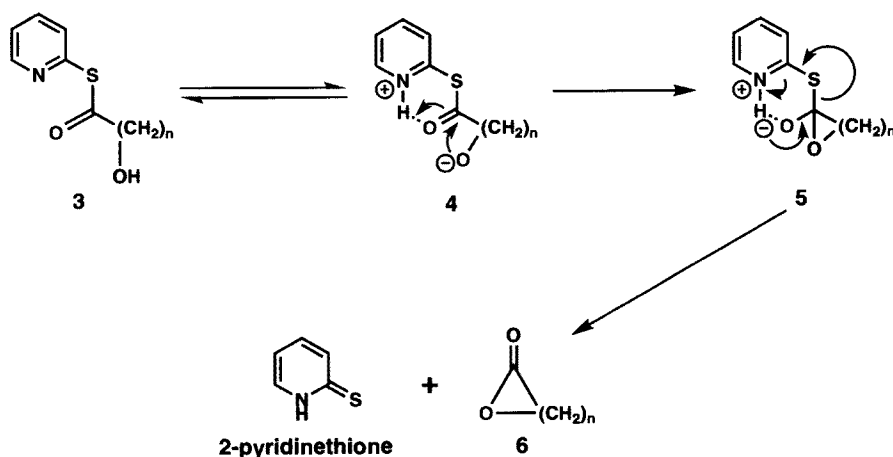
Erythronolide B (**1**) is an exceedingly complex target molecule. Organized around the periphery of its 14-membered lactone ring are ten asymmetric carbon atoms, five of which are arranged consecutively in a single chain. In response to the synthetic challenge presented by erythromycin A (**2**), R.B. Woodward wrote, characteristically, in 1956, "Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."² Although the structure of **1** and its relatives were known for some time,³ progress in the arena of organic synthesis was severely hampered by a shortage of efficient synthetic methodology for the construction of large ring lactones. Thus, even if one could cope with the wealth of asymmetric carbon atoms contained within erythronolide B, the state of the art in organic synthesis methodology was not equal to the task of constructing large-ring lactones before the mid 1970s.

Challenged and inspired by the complex structures of the erythromycins, Corey's group developed a novel, efficient, and general



2: erythromycin A

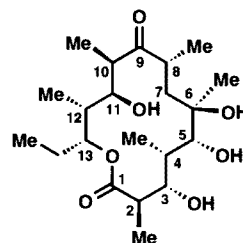
method for the synthesis of large-ring lactones which has had a stimulating and lasting influence on the macrolide field.⁴ This method, known as the Corey–Nicolaou double activation method, permits the lactonization of hydroxy acids under mild conditions, and it has performed admirably in the context of partial and total syntheses of a number of complex natural products.⁵ The development of this cyclization procedure was guided by the following considerations: (a) since the rate of lactone ring formation slows markedly as the length of the tether connecting the terminal hydroxyl and carboxyl groups increases, undesirably high temperatures and/or excessively high dilutions would be required unless some means were to be found to activate the reacting groups; (b) one way of simultaneously activating both the carboxyl and hydroxyl groups for mutual interaction would be to utilize a carboxylic acid derivative that would favor a proton transfer from the hydroxyl group to the carboxylic oxygen. This event would afford a more nucleophilic oxygen, and, at the same time, enhance the electrophilic character of the carbonyl carbon of the carboxylic acid derivative. Scheme 1 illustrates, for the specific case of a 2-pyridinethiol ester of a hydroxy acid **3**, the general features of the Corey–Nicolaou double activation method. The basic premise is that the pyridine nitrogen atom in **3** would facilitate a proton transfer from the hydroxyl group to the carbonyl group to give dipolar intermediate **4** (or its hydrogen-bonded equivalent). With a nucleophilic alkoxide and an activated carbonyl group, intermediate **4** could participate in a facile, electrostatically driven cyclization to **5**, which then would collapse yielding lactone **6** and 2-pyridinethione. Although intermolecular oligomerizations are possible, it was found that high-dilution procedures permit the formation of medium- and large-ring lactones in good to excellent yields from 2-pyridinethiol esters of a



Scheme 1. The Corey–Nicolaou macrolactonization strategy.

series of ω -hydroxy acids. Interestingly, thioesters that have no opportunity to form hydrogen-bonded intermediates of the type illustrated in **4** (i.e. when the pyridine nucleus is replaced by a phenyl ring) do not cyclize on heating in the absence or presence of base.⁶

The first total synthesis of erythronolide B (**1**) by Corey stands as an event of great historical significance in synthetic chemistry; it provides a powerful illustration of the utility of Corey's methods of macrolactonization and it demonstrates, in a particularly insightful way, the value of using readily accessible six-membered ring templates for the assembly of contiguous arrays of stereogenic centers.

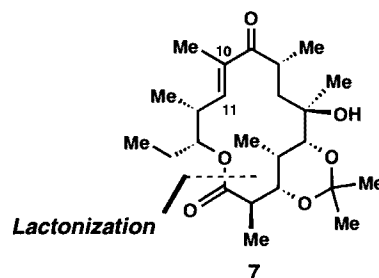


1: erythronolide B

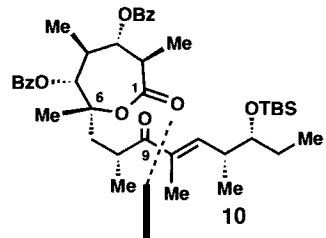
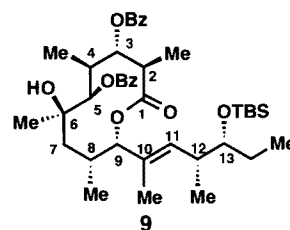
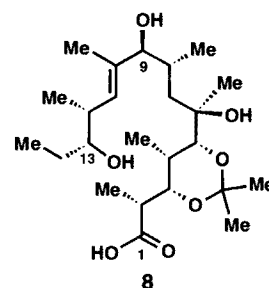
11.2 Retrosynthetic Analysis and Strategy

The general features of Corey's erythronolide B synthesis are summarized in Scheme 2. We begin our analysis with intermediate **7**, a substance which is closely related to erythronolide B (**1**). This key intermediate possesses the requisite 14-membered lactone ring and an appropriately placed π bond which can support the introduction of the remaining two stereocenters at carbons 10 and 11. Retrosynthetic cleavage of the indicated bond in **7** furnishes seco acid **8** as a viable predecessor. In the forward sense, simultaneous activation of the terminal hydroxyl and carboxyl groups could, in principle, induce an internal esterification or lactonization reaction to give the requisite 14-membered lactone ring. An oxidation of the C-9 hydroxyl group would then complete the formation of **7** from **8**. Intermediate **8** could be derived from **9** through a straightforward sequence of reactions. In the forward sense, cleavage of the lactone ring in **9**, followed by a few functional group manipulations, could secure the formation of **8**.

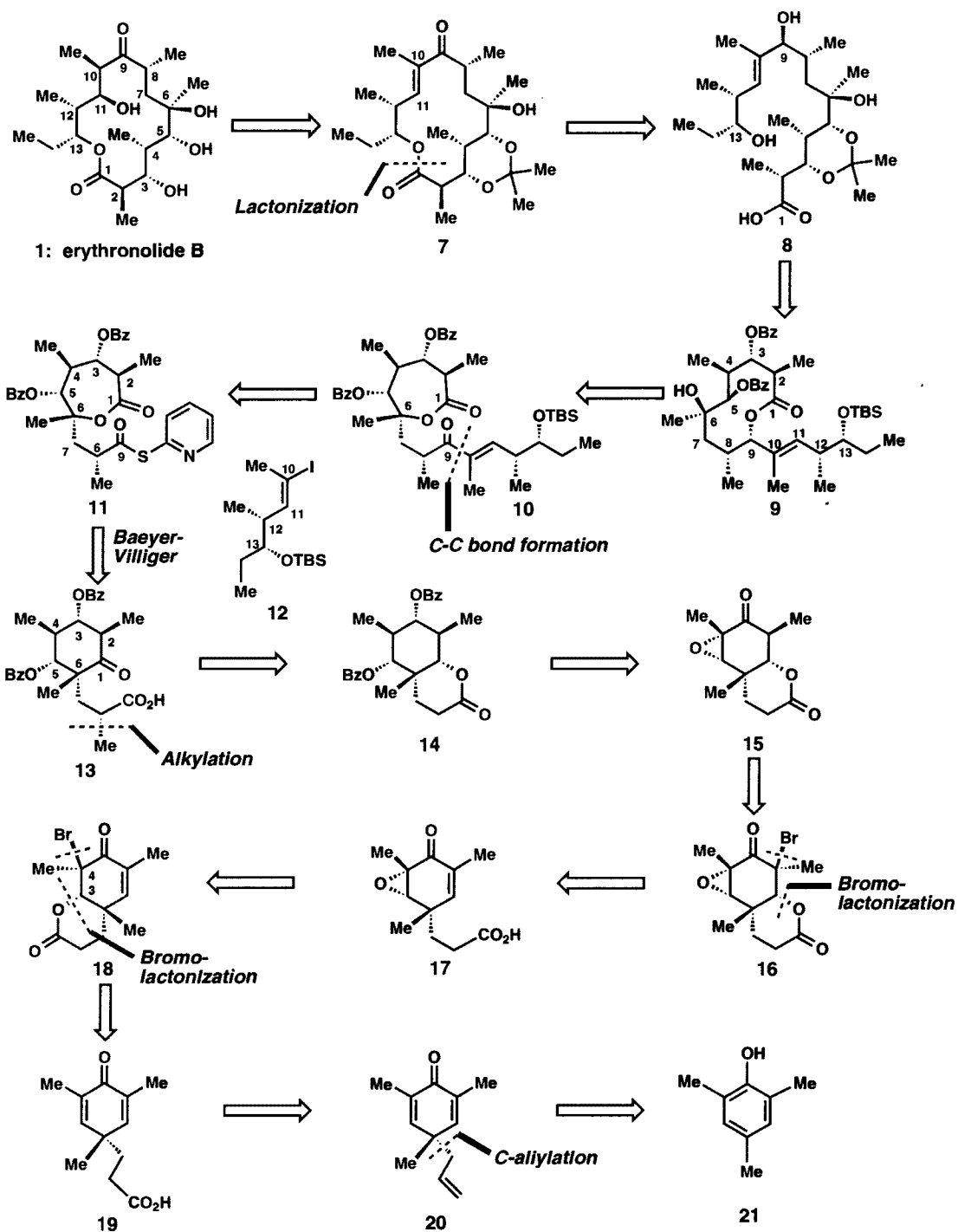
There is an interesting relationship between intermediates **9** and **10**. A chemoselective reduction of the ketone carbonyl at C-9 in **10** would afford a secondary hydroxyl group which would find itself in proximity to the carbonyl group of the lactone ring, and it is conceivable that this hydroxyl group could initiate a translactonization reaction to give intermediate **9**. Retrosynthetic disassembly of intermediate **10** by cleavage of the indicated carbon-carbon bond furnishes intermediates **11** and **12** as potential precursors, and allows considerable structural simplification. Intermediate **11** possesses significant electrophilic potential by virtue of the presence within its structure of a thiopyridyl ester. Intermediate **12**, on the other hand, is a suitable precursor for a nucleophilic organometallic reagent. A halogen-metal exchange reaction would allow conversion of **12** into a vinyl organometallic reagent which could react chemoselectively, in the forward sense, with the more reactive thiopyridyl ester carbonyl group to give intermediate **10**.



Lactonization



C-C bond formation



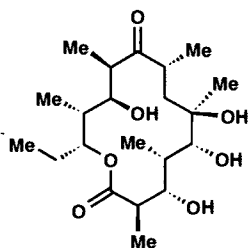
Scheme 2. Retrosynthetic analysis of erythronolide B (1).

The synthetic problem is now reduced to the preparation of two key intermediates, **11** and **12**. The thiopyridyl ester moiety in **11** will serve as the electrophile in a coupling reaction with a nucleophilic derivative of **12**, and it can be derived in one step from a carboxyl group. Another salient structural feature of **11** is the ϵ -lactone ring. Whenever faced with the challenge of constructing a lactone ring, one should always be mindful of the Baeyer–Villiger transform.⁷ When cyclic ketones are subjected to a Baeyer–Villiger reaction, they undergo oxidation to lactones with concomitant expansion of the ring by one atom.⁸ If an unsymmetrical cyclic ketone is employed in a Baeyer–Villiger reaction, an oxygen atom is, in many instances, inserted regioselectively between the carbonyl group and the carbon most able to bear a positive charge with retention of configuration. The Baeyer–Villiger reaction is, therefore, a very valuable method in organic synthesis because it is both regioselective and stereospecific. Application of this transform to the seven-membered lactone **11** furnishes the unsymmetrically substituted six-membered cyclic ketone **13** as a potential precursor.

Intermediate **13** is still very complex, particularly with respect to stereochemistry; all of the sp^3 -hybridized carbon atoms that compose the six-membered ring in **13** are stereogenic, and one is quaternary. On the basis of a cursory examination of its structure, it would appear that a synthesis of **13** would impose great demands on the methods of stereoselective synthesis. The development of an exceedingly efficient and elegant strategy for the diastereoselective assembly of **13** is one of the most outstanding features of Corey's synthesis. It was projected that intermediate **13** could be elaborated in a straightforward way from lactone **14**. In the synthetic direction, hydrolytic cleavage of the δ -lactone ring in the methylated form of **14**, followed by oxidation of the secondary hydroxyl group could give **13**. If we work our way back to intermediate **16**, via compound **15** we find that the stereochemical situation has hardly been simplified. After all, intermediate **16** possesses five contiguous asymmetric carbon atoms, three of which are fully substituted.⁹ There is, however, in intermediate **16**, an interesting functional group relationship that satisfies the prerequisite for the well-known and productive halolactonization transform. Retrosynthetic disconnection of the indicated bonds in **16** furnishes intermediate **17** as a potential precursor. In the forward sense, exposure of **17** to bromine could induce a bromolactonization reaction¹⁰ to give intermediate **16**. In this reaction, bromine would likely engage the olefin diastereoface that is opposite to the propionic acid side chain to give a transient bromonium ion which could then be intercepted intramolecularly by the proximal carboxyl group. The strong stereoelectronic preference for a stereospecific, *trans* diaxial addition to the carbon–carbon double bond¹¹ would guide the formation of **16**. Interestingly, intermediate **17** could conceivably be obtained in one step from intermediate **18**. Saponification of the δ -lactone ring in **18** would afford a secondary alkoxide at one terminus which could attack the adjacent C-4 position with concomitant dis-

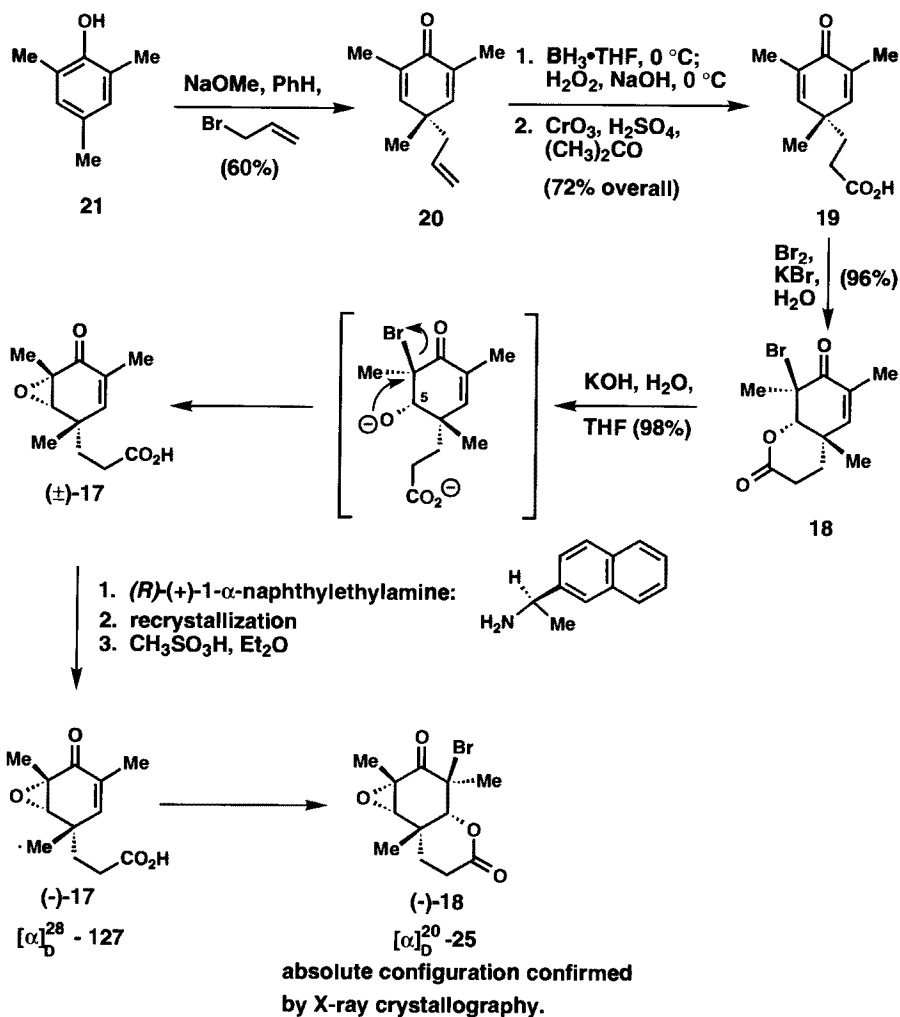
placement of bromide and inversion of configuration to give **17**. It will be noted that intermediate **18** possesses the requisite structural features for a second bromolactonization reaction. The vicinal bromine and lactone groups in **18** constitute the retron for the bromolactonization transform.⁷ Thus, cleavage of the indicated bonds in **18** gives prochiral dienone acid **19** as a potential precursor. Subjection of **19** to a bromolactonization reaction would convert both sp^2 -hybridized carbon atoms of one of the two π bonds into asymmetric carbon atoms. Through the application of successive bromolactonization transforms and straightforward functional group manipulations, a very complex stereochemical problem can be simplified in a most dramatic fashion. Through simple functional group transformations, intermediate **19** could originate from **20**, the projected product of a *C*-allylation of commercially available 2,4,6-trimethylphenol (**21**).

11.3 Total Synthesis



1: erythronolide B

The Corey synthesis of erythronolide B (**1**) commences with a regioselective *C*-alkylation of 2,4,6-trimethylphenol (**21**) (see Scheme 3). Employing a known procedure,¹² treatment of a solution of **21** in benzene with sodium methoxide and allyl bromide results in a regioselective allylation of the *para* position to give dienone **20** in a yield of 60%. Selective hydroboration of the monosubstituted vinyl group in **20** with borane gives, after oxidative workup and Jones oxidation of the primary hydroxyl group, dienone acid **19** in an overall yield of 72%. Intermediate **19**, an interesting symmetrical molecule, participates in a smooth bromolactonization reaction in the presence of bromine and potassium bromide to give racemic bromolactone **18** as a crystalline solid in an excellent yield of 96%. In this reaction, bromine reacts with one of the two enantiotopic π bonds to afford a transient bromonium ion which is then intercepted by the proximal propionate side chain. During the course of the bromolactonization reaction, the symmetry of **19** is broken, resulting in the creation of three stereogenic centers. Saponification of the δ -lactone ring in **18** with potassium hydroxide furnishes a carboxylate at one end of the point of cleavage and an α -disposed secondary alkoxide at the other. The alkoxide at C-5 is ideally situated, with respect to the adjacent carbon–bromine bond, for an internal S_N2 displacement reaction to give epoxy keto acid **17** after acidification. It was possible, at this stage, to obtain intermediate **17** in enantiomerically pure form through a resolution of the 1:1 mixture of diastereomeric ammonium salts that forms when (\pm)-**17** is treated with (*R*)-(+)-1- α -naphthylethylamine. Although enantiomerically pure **17** with the absolute configuration required for a synthesis of natural erythronolide B could be obtained after recrystallization and acidification,



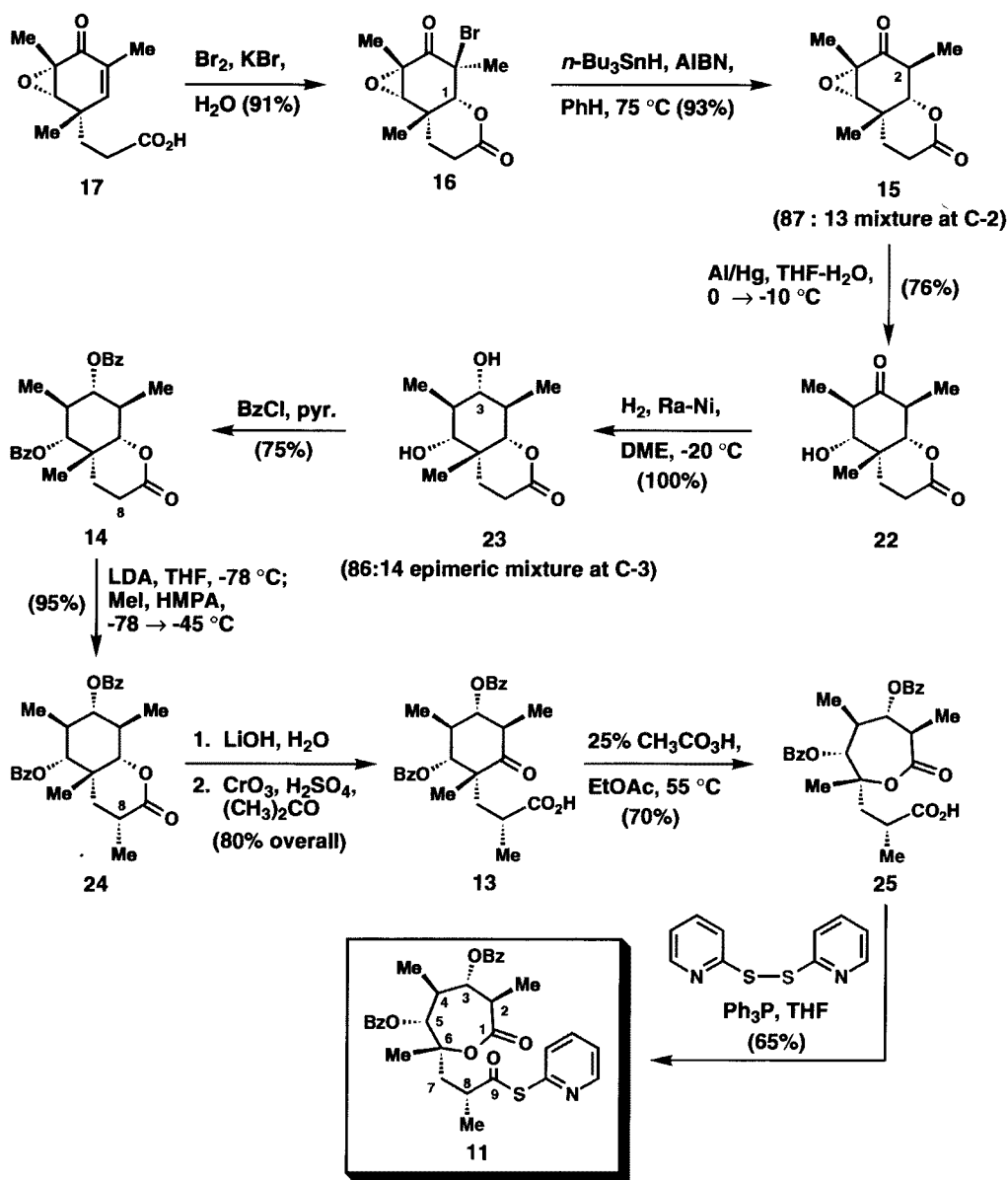
Scheme 3. Synthesis and resolution of compound 17.

it was found to be more convenient to proceed with the synthesis using racemic intermediates and defer a resolution to a later stage.

Of course, intermediate **17** is suitably functionalized for a second bromolactonization reaction (see Scheme 4). In the event, when an aqueous solution of the potassium salt of (\pm)-**17** is treated with bromine and potassium bromide, bromolactonization takes place, again with impressive facility, giving (\pm)-**16** in a yield of 91 %. This reaction creates two additional stereogenic centers, and also achieves the oxygenation of C-1. When a solution of **16** in benzene is treated with tri-*n*-butyltin hydride and a catalytic amount of the radical initiator azobisisobutyronitrile (AIBN), reductive cleavage of the carbon-bromine bond occurs to give intermediate **15** as an 87:13 mixture of diastereomers, epimeric at the indicated center, in a yield of 93 %. Separation of the stereoisomeric mixture was not necessary at this stage. The action of excess aluminum amalgam on crude **15** induces cleavage of the α -carbon-oxygen bond and furnishes racemic hydroxy ketone **22** as a diastereomerically pure crystalline solid after recrystallization from ethyl acetate. Hydrogenation of the carbon-oxygen π bond in **22** using neutral Raney nickel (Ra-Ni) in dry dimethoxyethane in an atmosphere of hydrogen affords, in quantitative yield, diol **23** together with a small amount (*ca.* 14 %) of the undesired diastereomer, epimeric at the newly formed stereocenter (C-3). Treatment of a solution of crude **23** in pyridine with excess benzoyl chloride gives, after recrystallization from ether, pure bisbenzoate **14** to the extent of 75 %. The evolution of a saturated cyclohexane ring which accommodates six substituents (see intermediate **14**), arranged properly in space, from a simple and readily available aromatic compound is a remarkable achievement. In only a handful of steps, all of the carbon atoms that constitute the planar aromatic ring in **21** are converted into unsymmetrically substituted tetrahedral carbon atoms in a manner that secures correct relative stereochemical relationships for an eventual synthesis of erythronolide B (**1**).

An important task remaining is the stereocontrolled introduction of a methyl group at C-8. When a cold (-78°C) solution of **14** in THF is treated successively with LDA and methyl iodide and then warmed to -45°C , intermediate **24** admixed with minor amounts of the C-8 epimer is formed in a yield of 95 %. The action of LDA on **14** generates a lactone enolate which is alkylated on carbon in a diastereoselective fashion with methyl iodide to give **24**. It is of no consequence that **24** is contaminated with small amounts of the unwanted C-8 epimer because hydrolysis of the mixture with lithium hydroxide affords, after Jones oxidation of the secondary alcohol, a single keto acid (**13**) in an overall yield of 80 %. Apparently, the undesired diastereoisomer is epimerized to the desired one under the basic conditions of the saponification step.

To complete the synthesis of key intermediate **11**, the ϵ -lactone ring must be formed and the carboxyl group must be converted into

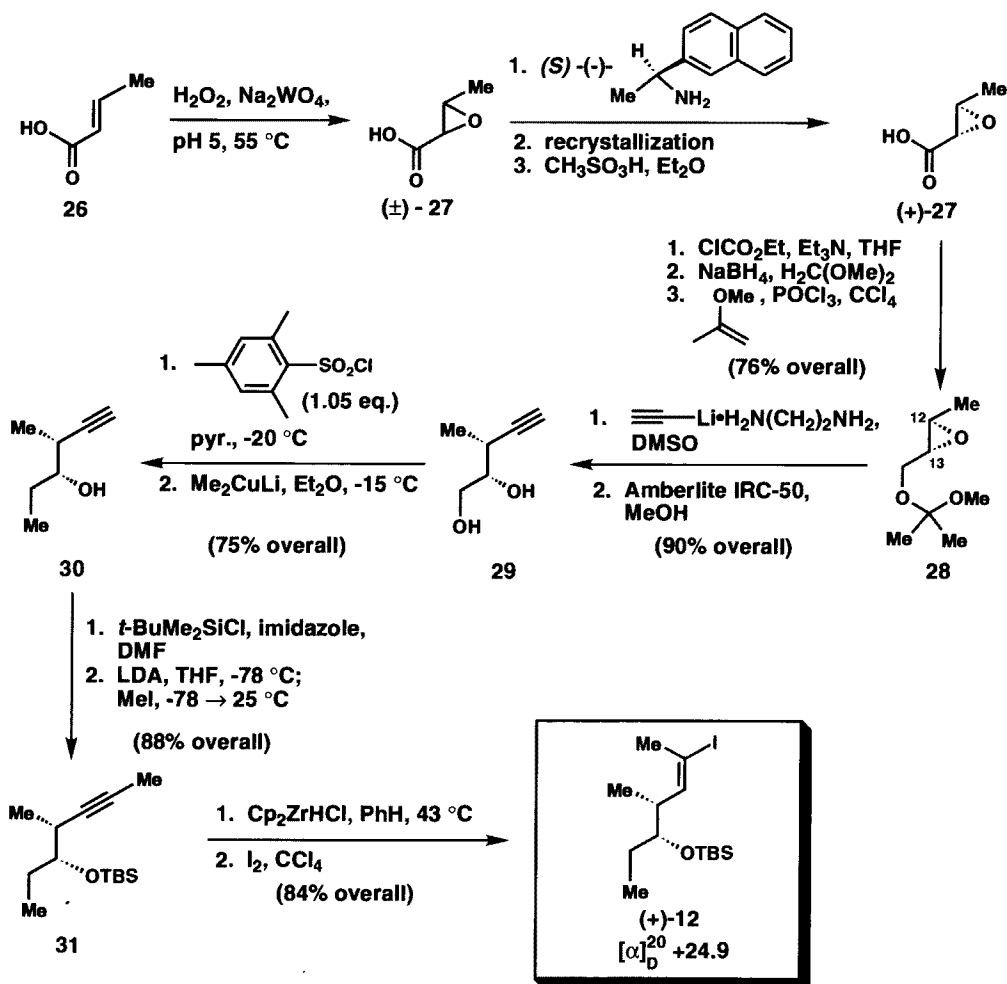


Scheme 4. Synthesis of intermediate 11.

the more electrophilic 2-pyridinethiol ester. After some careful experimentation, it was discovered that an excess of 25 % peracetic acid in ethyl acetate can, after a period of about six days at 55 °C, accomplish a Baeyer–Villiger oxidation of **13** to ϵ -lactone **25** in a yield of 70 %. Treatment of a solution of **25** in THF at 20 °C with 1.1 equivalents of 2,2'-dipyridyldisulfide and 1.2 equivalents of triphenylphosphine¹³ gives, after removal of solvent and silica gel chromatography at 5 °C, racemic thiol ester **11** in a yield of 65 %.

The synthesis of key intermediate **12**, in optically active form, commences with the resolution of racemic *trans*-2,3-epoxybutyric acid (**27**), a substance readily obtained by epoxidation of crotonic acid (**26**) (see Scheme 5). Treatment of racemic **27** with enantiomerically pure (*S*)-(-)-1-*a*-naphthylethylamine affords a 1:1 mixture of diastereomeric ammonium salts which can be resolved by recrystallization from absolute ethanol. Acidification of the resolved diastereomeric ammonium salts with methanesulfonic acid and extraction furnishes both epoxy acid enantiomers in enantiomerically pure form. Because the optical rotation and absolute configuration of one of the antipodes was known, the identity of enantiomerically pure epoxy acid, (+)-**27**, with the absolute configuration required for a synthesis of erythronolide B, could be confirmed. Sequential treatment of (+)-**27** with ethyl chloroformate, excess sodium borohydride, and 2-methoxypropene with a trace of phosphorous oxychloride affords protected intermediate **28** in an overall yield of 76 %. The action of ethyl chloroformate on carboxylic acid (+)-**27** affords a mixed carbonic anhydride which is subsequently reduced by sodium borohydride to a primary alcohol. Protection of the primary hydroxyl group in the form of a mixed ketal is achieved easily with 2-methoxypropene and a catalytic amount of phosphorous oxychloride.

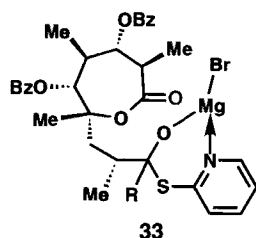
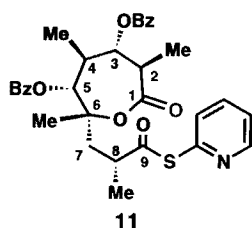
Although intermediate **28** possesses electrophilic potential at positions 12 and 13, carbon 13 is flanked by a sterically encumbered mixed ketal grouping and is, therefore, more hindered than C-12. When **28** is treated with lithium acetylide–ethylenediamine complex in DMSO at 25 °C, its oxirane ring is opened, and a new carbon–carbon bond is formed with inversion of configuration at C-12, giving 1,2-diol **29** after solvolysis of the mixed ketal grouping with Amberlite IRC-50 resin in methanol. The mixed ketal grouping in **28** thus fulfills the role of protecting group and guides the regiochemical course of the acetylide addition reaction. Although a small amount (~10 %) of the regioisomer arising from attack by acetylide at the more hindered C-13 position is obtained, it was found to be more convenient to carry the mixture forward and purify at a later stage. Selective conversion of the primary hydroxyl group in **29** into the corresponding mesitylsulfonate with mesitylenesulfonyl chloride and pyridine followed by treatment of the monosulfonate ester with lithium dimethylcuprate furnishes, after chromatographic purification on silica gel, intermediate **30** in a yield of 75 % from **29**. After protection of the secondary hydroxyl group in the form of a *tert*-butyldimethylsilyl ether, deprotonation



Scheme 5. Synthesis of intermediate (+)-12.

of the terminal alkyne with LDA, followed by quenching with methyl iodide, affords intermediate **31** in an overall yield of 88 %. A single isomeric vinyl iodide, the required intermediate **12**, is formed in 84 % yield through sequential alkyne hydrozirconation¹⁴ and iodination reactions.

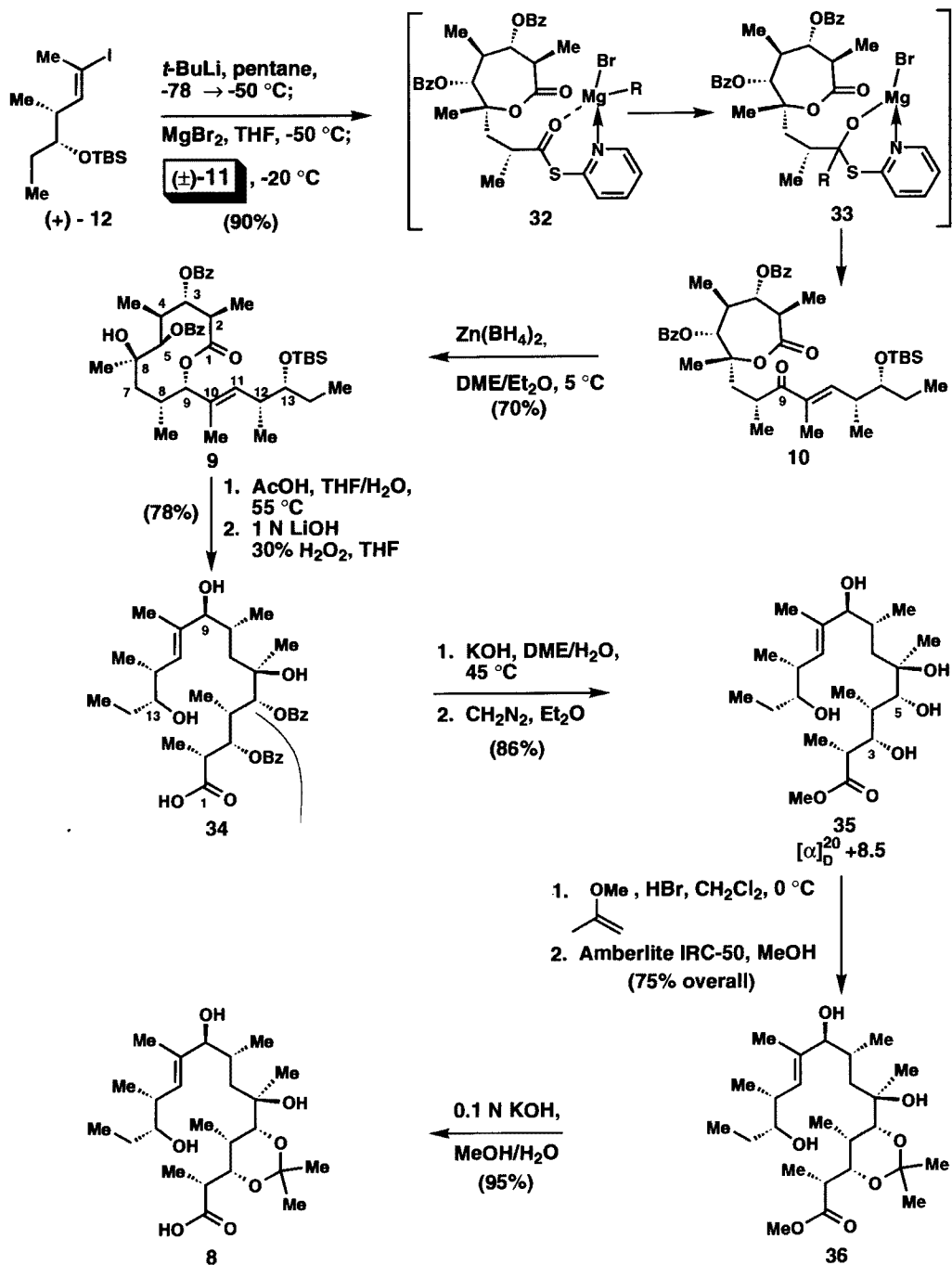
Having retraced the efficient and elegant sequences of reactions that have led to the synthesis of key intermediates **11** and **12**, we are now in a position to address their union and the completion of the total synthesis of erythronolide B. Taken together, intermediates **11** and **12** contain all of the carbon atoms of erythronolide B, and although both are available in optically active form of the required absolute configuration, racemic **11** and enantiomerically pure **12**



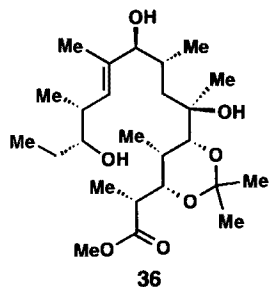
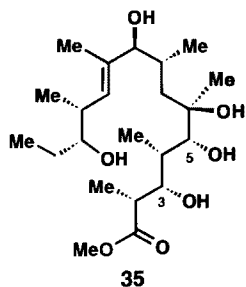
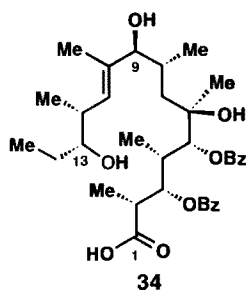
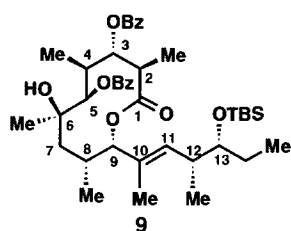
were employed in the synthesis. When a cold (-78°C) solution of vinyl iodide **12** in THF is treated with two equivalents of *tert*-butyllithium, a halogen-metal exchange reaction takes place and furnishes a vinyl lithium reagent which undergoes smooth conversion to a Grignard reagent after treatment with anhydrous magnesium bromide at -50°C (see Scheme 6). When this Grignard reagent is treated with 2-pyridinethiol ester (\pm)-**11**, it selectively attacks the thiol ester carbonyl group, affording ketone **10** after quenching with pH 7 buffer. Ketone **10** is produced as a 1:1 mixture of two diastereoisomers in an excellent yield of 90%.

It is instructive to digress and discuss this coupling reaction further. At first glance, the selective action of the Grignard reagent derived from vinyl iodide **12** on **11** may seem somewhat mysterious. After all, intermediate **11** possesses four carbonyl groups and each could potentially react with a strong nucleophile like a Grignard reagent. It is, however, important to recall that thiol esters are among the most electrophilic of the carboxylic acid derivatives. The inherent acylating potential of thiol esters closely approximates that of carboxylic acid anhydrides.¹⁵ Thus, on this basis, the selective action of a Grignard reagent on **11** would be expected. It is also interesting to note that a thiopyridyl ester can, in the presence of a Lewis acid like magnesium ion, participate in the formation of a six-membered cyclic chelate (see intermediate **32**). An internally chelated intermediate such as this should activate, even further, the thiol ester carbonyl for attack by a carbon nucleophile to give coordinated tetrahedral intermediate **33**. The reaction of 2-pyridinethiol esters with Grignard reagents to give ketones is very efficient and was originally developed by Mukaiyama and his coworkers.¹⁶ Mukaiyama's ketone synthesis is based on the premise that stabilization of a tetrahedral intermediate like **33** through coordination with magnesium ion should prevent further addition, and thus the formation of a tertiary alcohol by-product, by deferring the formation of the desired ketone product until aqueous workup.

The convergent union of intermediates **11** and **12** has accomplished the assembly of a molecule that possesses all of the carbon atoms of erythronolide B. Like intermediate **11**, compound **10** is the host of four carbonyl groups which could conceivably compete with each other for reaction with a nucleophilic reagent. Inherently, the ketone carbonyl at C-9 should be more reactive than the ϵ -lactone carbonyl and the two benzoate carbonyls. However, with the goal of achieving a selective reduction of the C-9 ketone carbonyl group, it was observed that most reducing agents either do not discriminate between the ketone and ϵ -lactone carbonyl groups, or exhibit a pronounced preference for a 1,4-reduction of the enone in **10**. Thus, it was only after a good deal of experimentation that it was eventually discovered that zinc borohydride will reduce the ketone carbonyl group at C-9, in a completely selective fashion and over the course of 72 hours, to give intermediate **9** in a 70% yield. The 1,2-reduction of the C-9 ketone carbonyl with zinc borohydride is completely stereoselective, and it affords a secondary alkoxide in



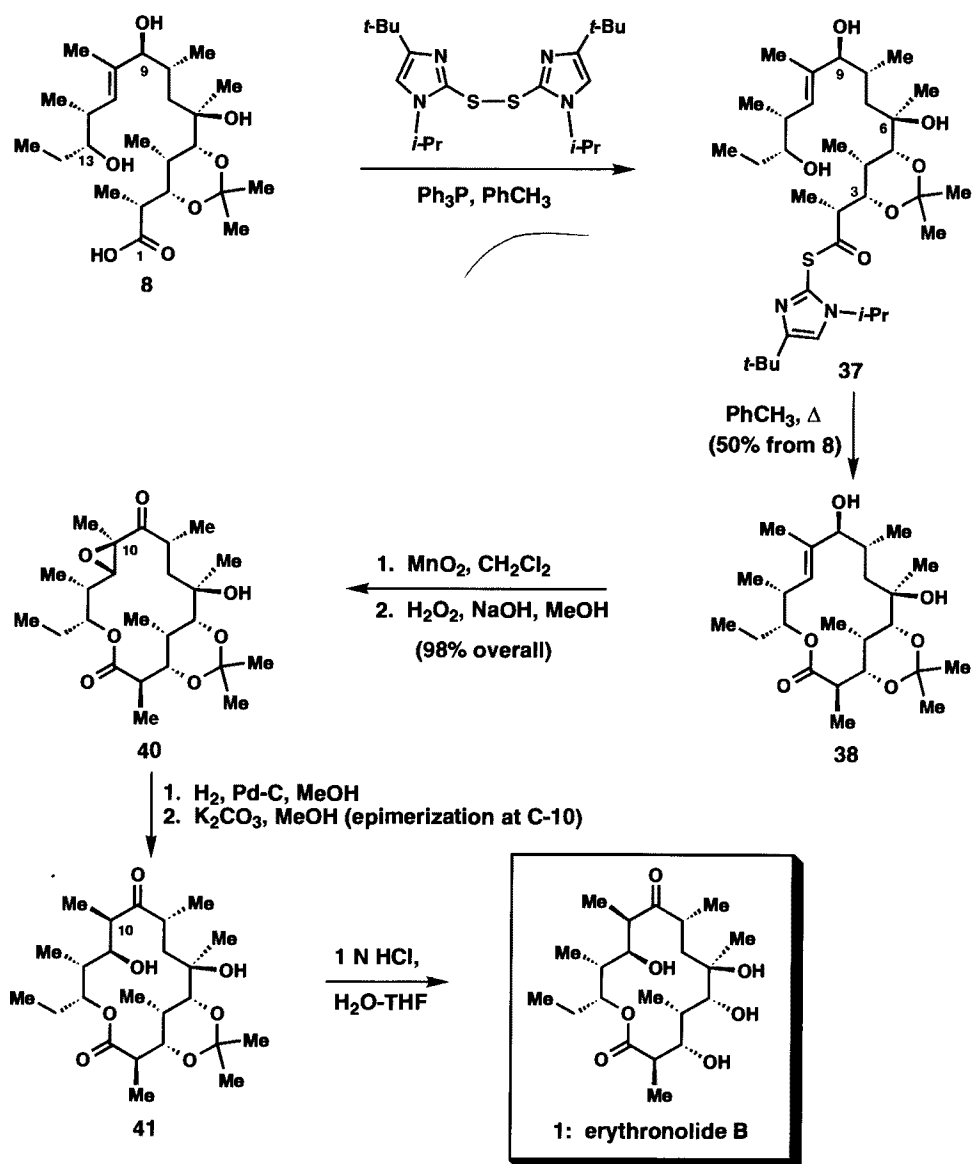
Scheme 6. Synthesis of intermediate 8.



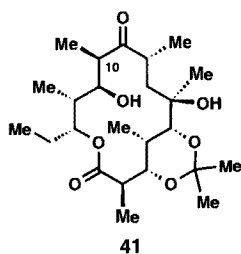
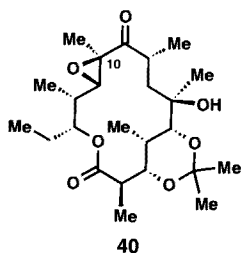
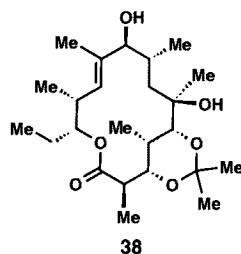
spatial proximity to the ε -lactone carbonyl. The alkoxide attacks the ε -lactone carbonyl group and initiates a translactonization or lactone migration reaction to give intermediate **9**. Removal of the C-13 *tert*-butyldimethylsilyl protecting group in **9** with acetic acid/water/THF (3:1:1) at 55 °C, followed by saponification of the ten-membered lactone ring with 30% hydrogen peroxide and 1*N* lithium hydroxide in THF at 20 °C, furnishes intermediate **34** in an overall yield of 78%. Hydrolytic cleavage of the two benzoate esters in **34** using excess potassium hydroxide in wet DME at 45 °C gives, after esterification of the carboxyl group with diazomethane, intermediate **35** and its diastereoisomer in a yield of 86%. It will be recalled that the coupling of intermediates (\pm)-**11** and (+)-**12** produced a 1:1 mixture of diastereoisomers which were taken forward and separated at this stage by silica gel chromatography. Intermediate **35** possesses the correct absolute configuration for a synthesis of **1**, and its identity was secured through comparison of its physical and spectroscopic properties with the same substance derived from natural erythronolide B (**1**). Simultaneous protection of the hydroxyl groups at carbons 3 and 5 in intermediate **35** in the form of an acetonide ring can be achieved easily with an excess of 2-methoxypropene and 0.5 equivalents of dry hydrogen bromide in methylene chloride at 0 °C. After selective solvolysis of the mixed ketal groupings, which formed at the other free hydroxyl groups, with Amberlite IRC-50 resin in methanol at 20 °C, acetonide ester **36** is obtained in a yield of 75% from **35**.

We have now reached a critical stage in the synthesis. The action of 0.1 *N* potassium hydroxide in 3:1 methanol:water on intermediate **36** at 45 °C induces smooth saponification of the methyl ester and gives acetonide hydroxy acid **8** in an excellent yield of 95%. Using Mukaiyama's procedure,¹³ **8** can be converted to thiol ester **37** with triphenylphosphine and 2,2'-bis-(4-*tert*-butyl-*N*-isopropyl)imidazoyl disulfide (see Scheme 7).¹⁷ Syringe pump addition of **37** to dry toluene at reflux over the course of 12 hours results in macro-lactonization, affording intermediate **38** in 50% yield. It is noteworthy that this cyclization was achieved without prior protection of the hydroxyl groups at C-6 and C-9, and that the imidazoyl reagent proved superior, in this instance, to the dipyridyl disulfide reagent discussed earlier.

It is interesting to speculate about the role of the C3–C5 acetonide ring of intermediate **37** in the cyclization reaction. This cyclic protecting group was selected with the hope that it would preorganize the open-chain hydroxy acid and thus facilitate ring closure. During the course of Woodward's elegant synthesis of erythromycin A (**2**),¹⁸ it was also found that cyclic protecting groups in the hydroxy acid cyclization substrate (seco acid) are required for efficient lactonization.^{18b} It was reasoned that such groups may induce the seco acid substrate to adopt a conformation resembling that of the corresponding lactone; such an event would have a very favorable impact on the lactonization reaction. With regard to Corey's synthesis of erythronolide B (**1**), it is interesting to note that the

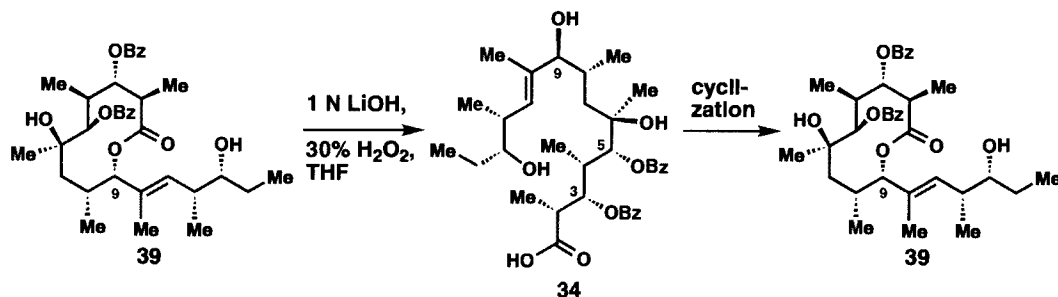


Scheme 7. Total synthesis of erythronolide B (1).



conversion of the ten-membered ring lactone **39** into **34**, followed by relactonization, affords **39** in high yield (see Scheme 8). No appreciable amount of the 14-membered ring lactone could be detected. Of course, intermediate **34** possesses benzoate esters at positions 3 and 5; its carbon backbone is not rigidified by any cyclic protecting groups. Thus, it is likely that the C3–C5 acetonide ring in **37** not only serves as a protecting group but also reduces rotational/conformational freedom of the carbon backbone and influences, in a favorable way, the desired lactonization to form the 14-membered ring lactone, as predicted.

The completion of the total synthesis of **1** only requires a few straightforward functional group manipulations.^{5a} Oxidation of the C-9 allylic alcohol in **38** with MnO_2 , followed by epoxidation of the C10–C11 enone double bond with basic hydrogen peroxide, gives epoxy ketone **40** in an overall yield of 98 %. It is likely that a strong preference for peripheral attack on the C10–C11 double bond by the oxidant enforces the formation of the desired epoxide **40**.¹⁹ Reduction of the oxirane ring with hydrogen over Pd–C catalyst in methanol furnishes, after epimerization at C-10 with potassium carbonate in methanol, intermediate **41**. Acid-catalyzed hydrolysis of the C3–C5 acetonide completes the total synthesis of erythronolide B (**1**).



Scheme 8. Macrolactonization of intermediate **34**.

11.4 Conclusion

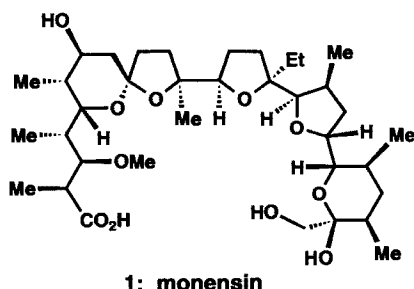
Corey's synthesis of erythronolide B (**1**) is a beautiful illustration of the traditional approach to the creation of consecutive arrays of stereogenic centers. Through a short sequence of reactions in which the bromolactonization reaction plays a commanding role, a simple, symmetrical aromatic ring is molded into a saturated six-membered ring which is laden with six contiguous asymmetric carbon atoms (see intermediate **14**). In addition, the formation of the oxygenated stereogenic center at C-6 through a regioselective and stereospecific Baeyer–Villiger oxidation, and the efficient coupling of intermediates **11** and **12**, an exercise in stereochemical correlation,²⁰ are both noteworthy transformations in this synthesis.

Natural product total syntheses are particularly valuable when they are attended by the development of general utility methods of synthesis. In some instances, the successful completion of a natural product total synthesis requires the development and application of a new synthetic method. The total synthesis of erythronolide B by Corey *et al.* is one of these instances. The double activation macro-lactonization method was a fruitful innovation that was introduced in response to the challenge presented by the macrocyclic structures of the erythromycins. Several other methods to achieve the same objective, and numerous applications followed.

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Monensin

12.1 Introduction

Ionophores constitute a large collection of structurally diverse substances that share the ability to complex cations and to assist in the translocation of cations through a lipophilic interface.¹ Using numerous Lewis-basic heteroatoms, an ionophore organizes itself around a cationic species such as an inorganic metal ion. This arrangement maximizes favorable ion–dipole interactions, while simultaneously exposing a relatively hydrophobic (lipophilic) exterior.

A salient subgroup of the naturally occurring ionophores is the polyether antibiotics.² This subgroup comprises a large number of structurally related molecules produced by various strains of *Streptomyces* organisms. Assembled principally from the elements carbon, hydrogen, and oxygen, the structures of the polyether antibiotics are very complex. These unique structures terminate at one end in a carboxyl group, and are further distinguished by a concatenation of cyclic ether rings (*i.e.* tetrahydrofuran and tetrahydropyran) and numerous stereocenters. In addition, many members of the polyether class contain one or more rigid spiroketal substructures.

In 1967 Agtarap *et al.* disclosed the isolation and structure of monensic acid (**1**).³ Compound **1**, now known as monensin, is produced by a strain of *Streptomyces cinamonensis*, and exhibits broad-spectrum anticoccidial activity. Since its introduction on the market in 1971, monensin has been used very successfully to combat coccidial infections in poultry and as an additive in cattle feed.⁴ In the polyether family, monensin occupies a position of some historical significance. Although monensin was the fifth polyether

antibiotic to be reported, it was the first member to be structurally characterized. The monensin molecule bears all of the structural features that distinguish the polyether class of antibiotics; it possesses the characteristic terminal carboxylic acid group, a 1,6-dioxaspiro[4.5]decane substructure, two tetrahydrofuran rings, and a functionalized tetrahydropyran ring. From the stereochemical point of view, the monensin molecule is particularly complex. Of the twenty-six carbon atoms constituting the backbone of the natural product, seventeen are stereogenic and six of these are contiguous.

Interestingly, in both crystalline and solution states, the monensin molecule assumes a cyclic structure which is maintained by two strong intramolecular hydrogen bonds between the terminal C-1 carboxyl group and the hydroxyl groups affixed to carbons 25 and 26 (monensin numbering see Figure 1). While monensin's exterior is almost completely hydrocarbon-like, its interior is lined with numerous Lewis-basic oxygen atoms. Monensin's unique cyclic conformation would thus appear to be ideally suited for the complexation of metal ions and the transportation of such ions into a lipophilic medium. Indeed, monensin and its relatives are high-affinity binders of inorganic cations, and they exert their biological effects by altering the distribution of cations across biological membranes.

It would be difficult to overestimate the role that the polyether antibiotics have played in the development of organic synthesis, particularly in the area of acyclic stereocontrol. These molecules have inspired many spectacular achievements in organic synthesis, achievements that have dramatically expanded the power and scope of the science. In fact, it would not be inaccurate to attribute much of our understanding about the factors controlling acyclic stereo-selectivity for such fundamental processes as hydroboration,⁵ epox-

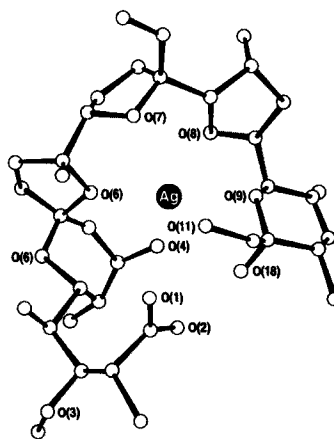
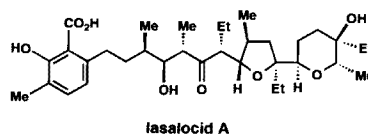


Figure 1. X-ray crystal structure of the monensin- Ag^+ complex (reprinted with permission from the American Chemical Society: *J. Am. Chem. Soc.* **1967**, *89*, 5737).

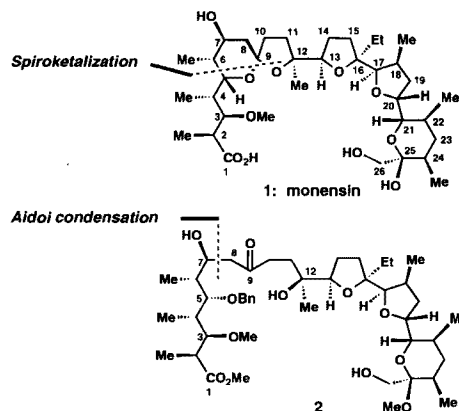
idation,⁶ and halocyclization⁷ of olefins, the Ireland enolate Claisen rearrangement,⁸ carbonyl addition reactions,⁹ and asymmetric aldol condensations¹⁰ to synthetic studies in the polyether field.¹¹ Less than one year after Kishi and coworkers disclosed their landmark synthesis of lasalocid A,^{12,13} the first synthesis of a polyether antibiotic, the Kishi group reported the first total synthesis of monensin (**1**).^{14,15} The latter achievement is noted for its convergency, and for the manner in which it exploits acyclic conformational control elements, allylic 1,3-strain in particular, to achieve stereochemical control in acyclic systems. The remainder of this chapter addresses Kishi's elegant chemical synthesis of the monensin molecule.

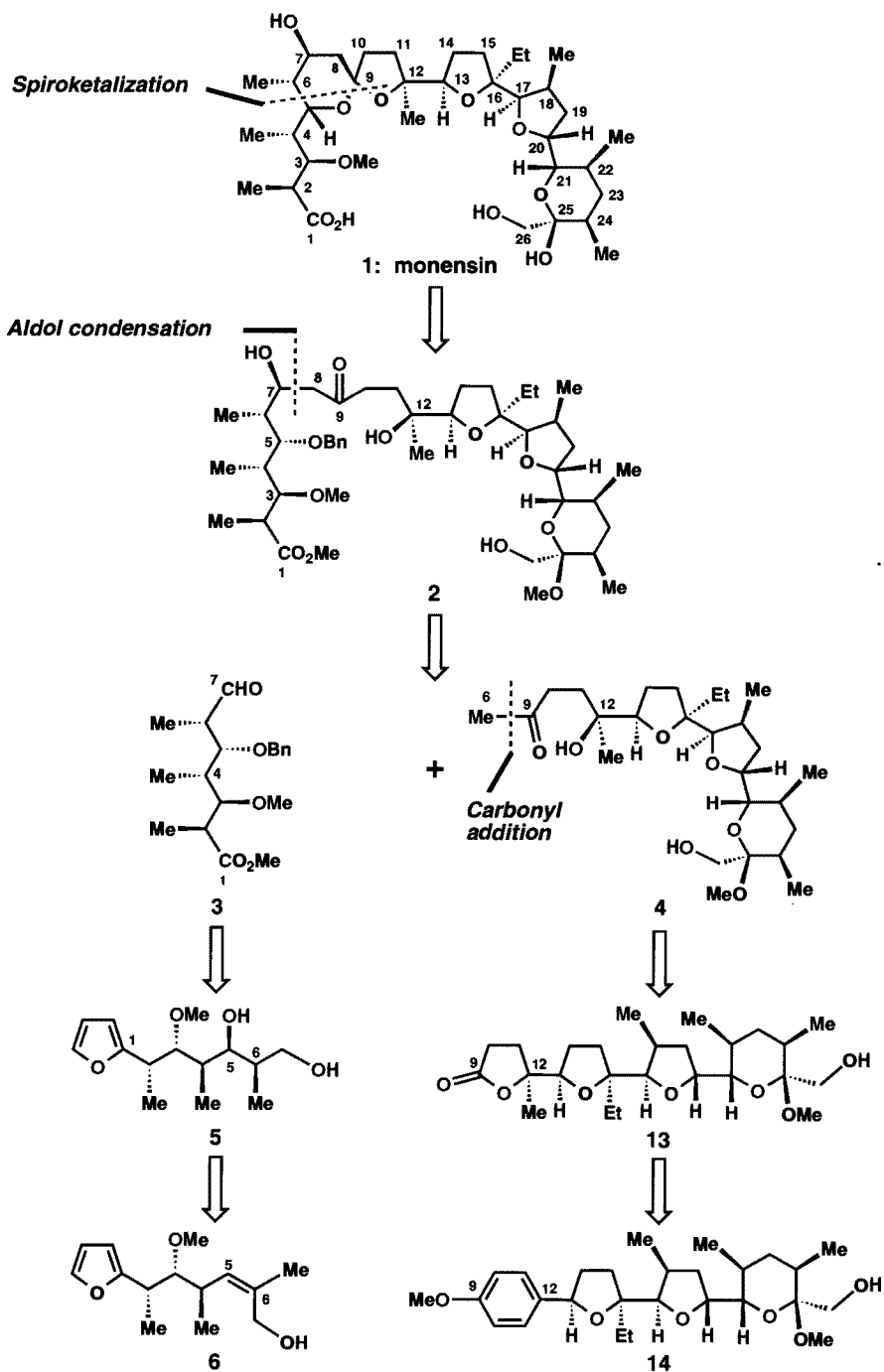


12.2 Retrosynthetic Analysis and Strategy

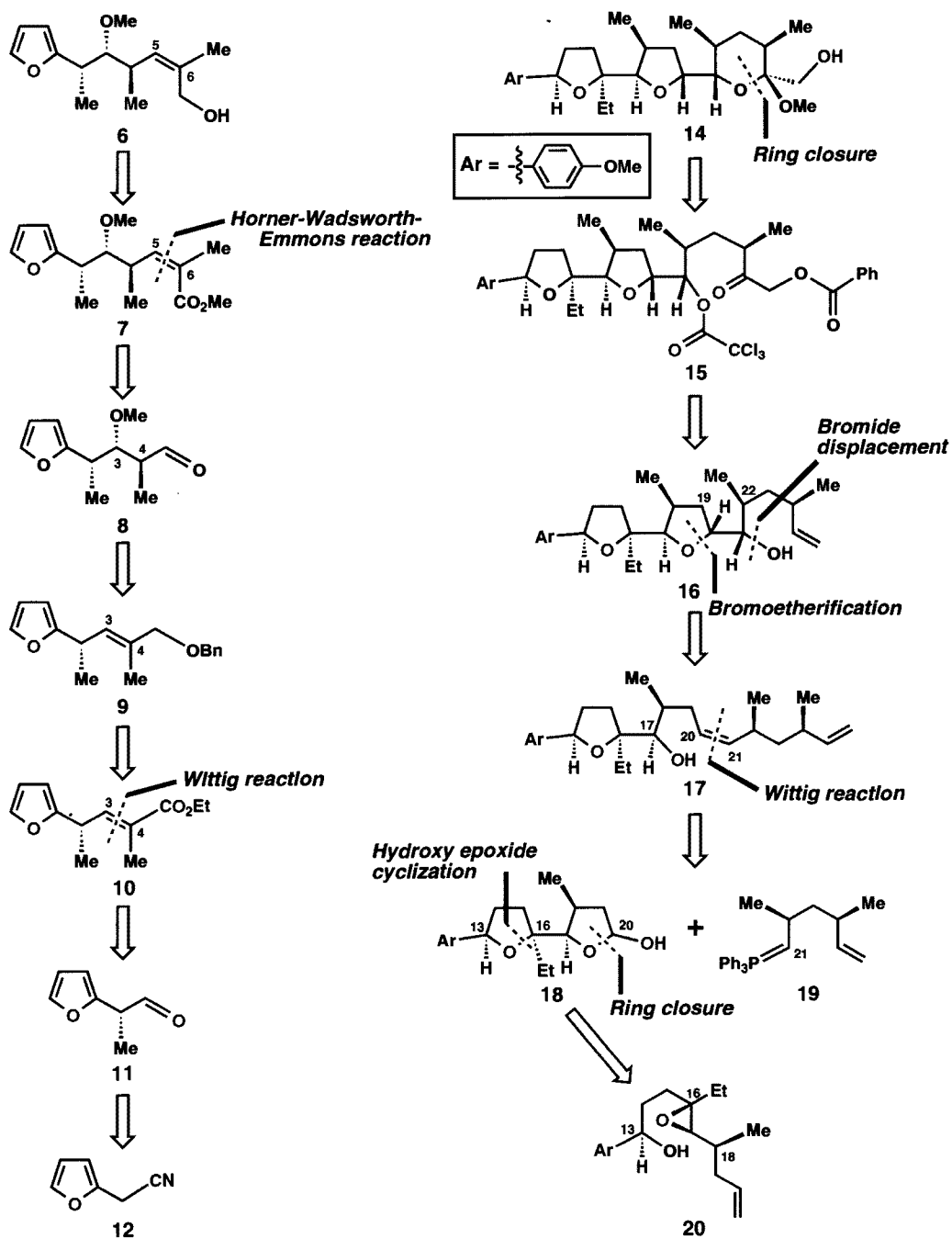
It would be instructive to begin by introducing two fundamentally distinct and frequently used strategies for the management of stereochemical relationships. The principle of *absolute asymmetric synthesis*,¹⁶ also known as *stereochemical correlation*,¹⁷ entails the coupling of prefabricated optically active building blocks. Provided that each building block is of the properly specified absolute configuration, then the relative stereochemical relationships that arise when these optically active fragments are joined must necessarily be the desired ones. On the other hand, when addressing the synthesis of a molecule that contains multiple stereocenters in proximity, it is often possible to exploit preexisting asymmetry for the purpose of establishing new asymmetry. Stereochemical control in this sense is referred to as *relative asymmetric induction*¹⁸ because a stereocenter(s) already present in the substrate molecule guides the introduction of a new stereocenter(s); the newly introduced asymmetric elements bear a specific relationship to previously existing ones. It is relevant to introduce these two strategies at this point because the Kishi group utilized both to cope with the wealth of stereogenic centers found in monensin (**1**).

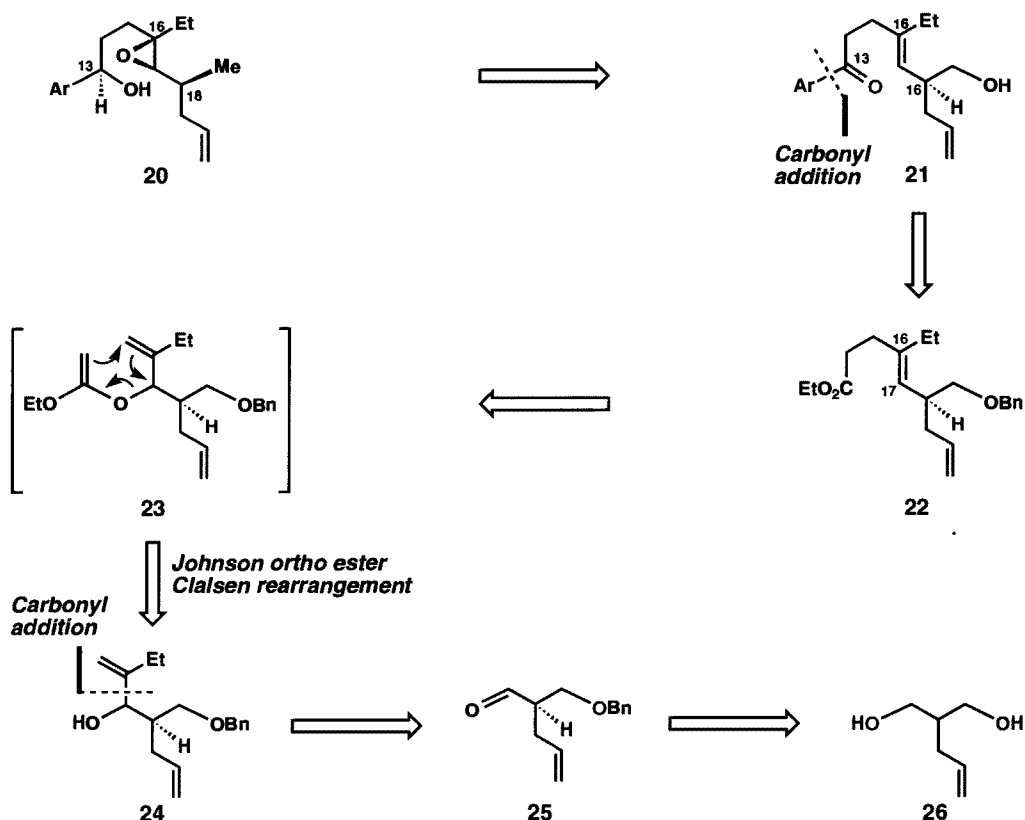
The general features of the monensin synthesis conducted by Kishi *et al.* are outlined, in retrosynthetic format, in Scheme 1. It was decided to delay the construction of monensin's spiroketal substructure, the 1,6-dioxaspiro[4.5]decane framework, to a very late stage in the synthesis (see Scheme 1). It seemed reasonable to expect that exposure of the keto triol resulting from the hydrogenolysis of the C-5 benzyl ether in **2** to an acidic medium could, under equilibrating conditions, result in the formation of the spiroketal in **1**. This proposition was based on the reasonable assumption that the configuration of the spiroketal carbon (C-9) in monensin corresponds to the thermodynamically most stable form, as is the case for most spiroketal-containing natural products.¹⁹ Spiroketal found in nature usually adopt conformations in which steric effects are minimized and anomeric effects are maximized.





Scheme 1. Retrosynthetic analysis of monensin (1).

**Scheme 1.** Retrosynthetic analysis of monensin (**1**) (continued).



Scheme 1. Retrosynthetic analysis of monensin (**1**) (continued).

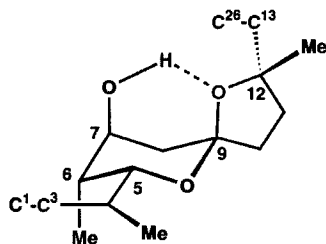


Figure 2. The monensin spiroketal moiety.

The prevailing situation in the case of monensin is interesting (see Figure 2). As expected, the C–O bond in the five-membered ring is axial to the six-membered ring, while the C–O bond of the pyran ring is roughly axial with respect to the five-membered ring; anomeric stabilization is thus maximized. With reference to Figure 2, it will be noted that although the C1–C4 side chain rests comfortably in an equatorial position, the C-6 methyl and C-7 hydroxyl groups are both axially disposed. The seemingly unfavorable axial orientation of the latter two groupings is, however, compensated by a stabilizing intramolecular hydrogen bond between the C-7 hydroxyl and the axial C–O spiroketal bond (see Figure 2).^{2,13c,20}

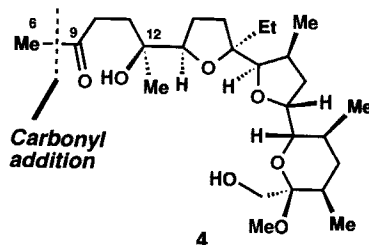
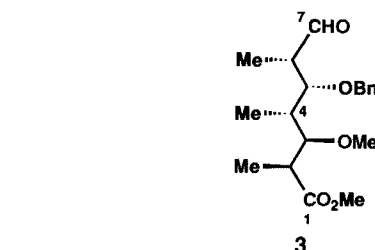
Key intermediate **2** (Scheme 1), complicated though it may be, is amenable to a retrosynthetic maneuver that significantly simplifies the synthetic problem. The β -hydroxy ketone unit in **2** constitutes

the retron for the aldol condensation transform.²¹ Thus, retrosynthetic cleavage of the indicated carbon–carbon bond provides compounds **3** and **4** as plausible precursors. In the synthetic direction, a convergent, intermolecular aldol condensation between the kinetic enolate derived from methyl ketone **4** and aldehyde **3** could accomplish the simultaneous creation of the C7–C8 bond and the hydroxyl-bearing C-7 stereocenter. Although key intermediate **3**, the left wing of the natural product, terminates at both ends with electrophilic functional groups, the C-7 aldehyde function is inherently more reactive, more susceptible to a nucleophilic attack than the C-1 methoxycarbonyl group. As a result, the convergent union of compound **3** and the kinetic enolate derived from **4** would be expected to take place chemoselectively through an aldol condensation, not through a Claisen condensation.

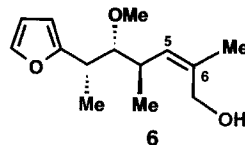
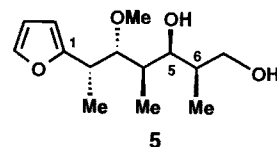
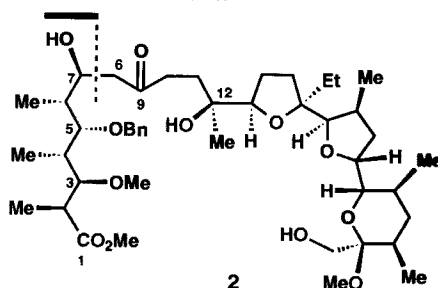
The issue of stereochemistry, on the other hand, is more ambiguous. *A priori*, an aldol condensation between compounds **3** and **4** could proceed with little or no selectivity for a particular aldol diastereoisomer. For the desired C-7 epimer (compound **2**) to be produced preferentially, the crucial aldol condensation between compounds **3** and **4** would have to exhibit Cram–Felkin–Anh selectivity^{22,23} (see **3** + **4** → **2**, Scheme 9). In light of observations made during the course of Kishi's lasalocid A synthesis,¹² there was good reason to believe that the preferred stereochemical course for the projected aldol reaction between intermediates **3** and **4** would be consistent with a Cram–Felkin–Anh model. Thus, on the basis of the lasalocid A precedent, it was anticipated that compound **2** would emerge as the major product from an aldol coupling of intermediates **3** and **4**.

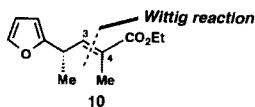
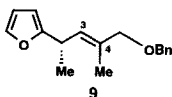
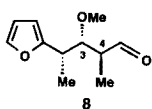
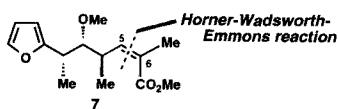
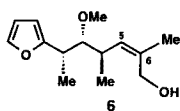
Compound **3**, the left-wing sector, possesses carbons 1–7 of the natural product and five contiguous stereocenters. In **3**, the proximity of many asymmetric carbon atoms could provide a worthy test for the principle of *stereospecific synthesis by induction* – “that is to say, the creation of new centres in a desired stereochemical sense under the directive influence of chiral factors present in prior intermediates.”²⁴ Kishi *et al.* recognized that the relative stereochemical relationships and the particular arrangement of oxygenated groupings in **3** could be established by using two substrate-stereocontrolled hydroboration reactions. Through a short sequence of functional group manipulations, compound **3** could be derived from intermediate **5**. The conspicuous furan nucleus in **5** is to serve as a stable substitute for a terminal carboxyl group; the furan nucleus is, in fact, an effective surrogate for a carboxyl group because it is inert to many reaction processes, and yet it can be smoothly converted to a carboxyl group by a straightforward oxidative cleavage reaction.^{25,26}

Application of the hydroboration transform to intermediate **5** provides unsaturated alcohol **6** as a potential precursor. In the synthetic direction, a regio- and stereocontrolled hydroboration/oxidation of the $\Delta^{5,6}$ double bond in **6** could accomplish the simultaneous introduction of the adjacent C-5 hydroxyl- and C-6 methyl-bearing



Aldol condensation





stereocenters. As a method for the functionalization of alkenes, the hydroboration/oxidation process is extremely valuable for the following reasons: (1) it is, in many instances, highly regioselective; (2) the hydroboration step is stereospecific (*syn* addition); and (3) stereochemistry is retained in the oxidation step. A most important consequence of the stereospecific nature of the hydroboration/oxidation process is that it is possible to define relative stereochemical relationships in the product simply by controlling the geometry of the substituted alkene in the starting material; stereochemical control in this sense is referred to as *internal asymmetric induction*.¹⁸ The *cis* geometry of the double bond in **6** is, therefore, crucial because it determines the *syn* C5–C6 stereorelationship in **5**. If, on the other hand, the olefin geometry in **6** were *trans*, the hydroboration/oxidation reaction would furnish a product in which the relative orientation of hydroxyl and methyl groups is *anti*. The hydroboration/oxidation of **6** would thus constitute an example of a stereospecific transformation because there would be a correspondence between product stereochemistry and starting material stereochemistry. In other words, stereoisomeric starting materials would afford stereoisomeric products.

Unsaturated ester **7**, the projected precursor of **6**, could be formed in one step from aldehyde **8** through a *cis*-selective Horner–Wadsworth–Emmons reaction. Aldehyde **8**, a substance with three contiguous stereocenters, could, in principle, be fashioned in a straightforward manner from compound **9**. It was presumed that compound **9** would adopt a reasonably well-defined conformation in the vicinity of the $\Delta^{3,4}$ double bond, a conformation that minimizes destabilizing allylic 1,3-strain (see **9a**, Scheme 2).²⁷ In conformer **9a**, the $\Delta^{3,4}$ double bond is flanked by two different substituents, and it was anticipated that a hydroboration reaction would take place across the more accessible olefin diastereoface, the face opposite to the furan ring. In this manner, the C-2 stereocenter in **9** would guide the stereochemical course of the hydroboration event (relative asymmetric induction), whereas the *anti* C3–C4 relative stereorelationship in the product would be dictated by the *trans* olefin geometry in **9** (internal asymmetric induction). A few conventional functional group manipulations could then complete the synthesis of **8** from **9**.

Because the olefin geometry in compound **9** will most certainly have a bearing on the stereochemical outcome of the hydroboration step, a reliable process for the construction of the *trans* trisubstituted olefin in **9** must be identified. *A priori*, the powerful and predictable Wittig reaction²⁸ could be used to construct *E* α,β -unsaturated ester **10** from aldehyde **11**. Reduction of the ethoxycarbonyl grouping in **10**, followed by benzylation of the resulting primary alcohol, would then complete the synthesis of **9**. Aldehyde **11** is a known substance that can be prepared from 2-furylacetonitrile (**12**).

Methyl ketone **4** (Scheme 1), the right-wing sector of monensin (**1**), possesses nineteen of the twenty-six carbon atoms that constitute the backbone of the natural product. Compound **4** is distin-

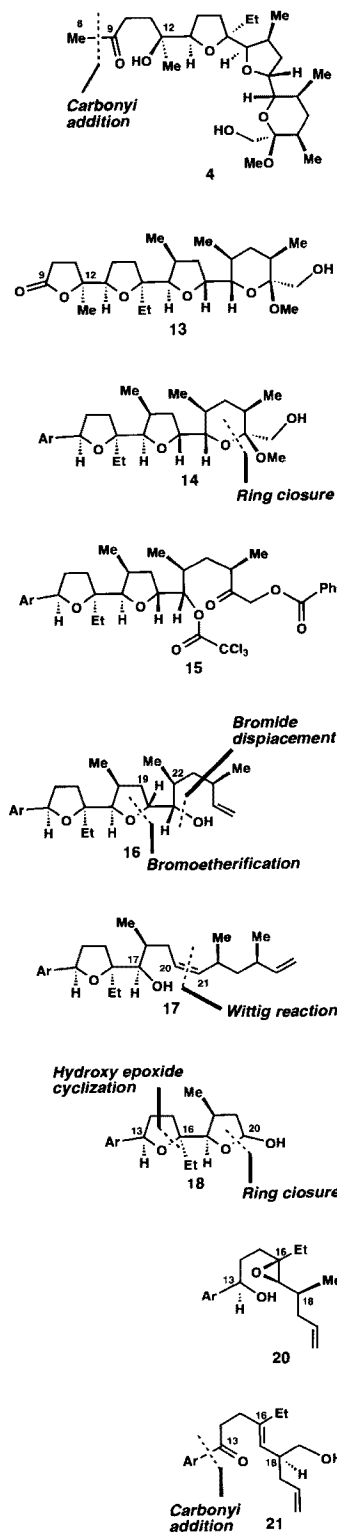
guished by ten stereocenters and a linear arrangement of two tetrahydrofuran rings and one tetrahydropyran ring – a very impressive structure. In principle, this substance could be derived in one step from compound **13**. The C-9 γ -lactone carbonyl in **13** is electrophilic and would undergo addition in the presence of a reactive organometallic reagent such as methyl lithium. The targeted methyl ketone **4** would then be revealed after collapse of the tetrahedral intermediate. Although it may not be obvious at this stage, the γ -lactone ring in **13** could be fashioned from an electron-rich aromatic nucleus (see intermediate **14**).

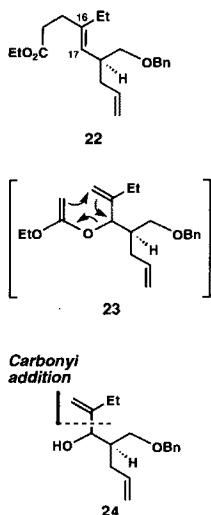
Retrosynthetic disassembly of the tetrahydropyran ring in **14**, a mixed cyclic ketal, provides ketone **15** as a plausible precursor. In the synthetic direction, the solvolytic cleavage of the ester functions in **15** would likely be attended by the formation of a cyclic hemi-ketal. On treatment with acidic methanol, this substance could then be converted to mixed ketal **14**.

Compound **16**, the projected precursor of **15**, could conceivably be assembled from bishomoallylic alcohol **17** via a pathway that features the oxidative functionalization of the $\Delta^{20,21}$ double bond with participation by the C-17 secondary hydroxyl. Compound **17** is an attractive retrosynthetic precursor for compound **16** because the $\Delta^{20,21}$ double bond, which could permit the introduction of the adjacent C-20 and C-21 stereocenters in **16**, provides a convenient opportunity for significant molecular simplification. Thus, retrosynthetic cleavage of the $\Delta^{20,21}$ double bond in **17** furnishes compounds **18** and **19** as potential building blocks. The convergent union of the latter two compounds through a Wittig reaction would be expected to afford **17** stereoselectively.

Although the constitution of compound **18** differs markedly from that of **20**, the transformation of the latter substance to the former would require nothing more than an acid-induced hydroxy epoxide cyclization and an oxidative cleavage of the terminal alkene. Hydroxy epoxide **20**, a substance that possesses four stereocenters, could conceivably be derived in short order from an intermediate around the C17–C18 bond in **21** would be controlled by allylic 1,3-strain (see conformer **21b**, Scheme 5). With an appropriately positioned primary hydroxyl group, it might be possible to carry out a hydroxyl-directed,²⁹ β face selective epoxidation of the more electron-rich $\Delta^{16,17}$ double bond using an electron-deficient oxidant such as *meta*-chloroperbenzoic acid (*m*CPBA). Reductive removal of the stereocontrolling hydroxyl function (or a derivative thereof) and reduction of the C-13 keto group would then complete the conversion of **21** to **20**.

A prominent structural feature of **21** and its precursor **22** is the *trans* C16–C17 trisubstituted double bond. The particular relationship between the ethoxycarbonyl function and the $\Delta^{16,17}$ double bond in **22** is significant because it satisfies the structural prerequisite for the Johnson ortho ester Claisen rearrangement transform.^{21,30} Mixed ketene acetal **23** thus emerges as the immediate





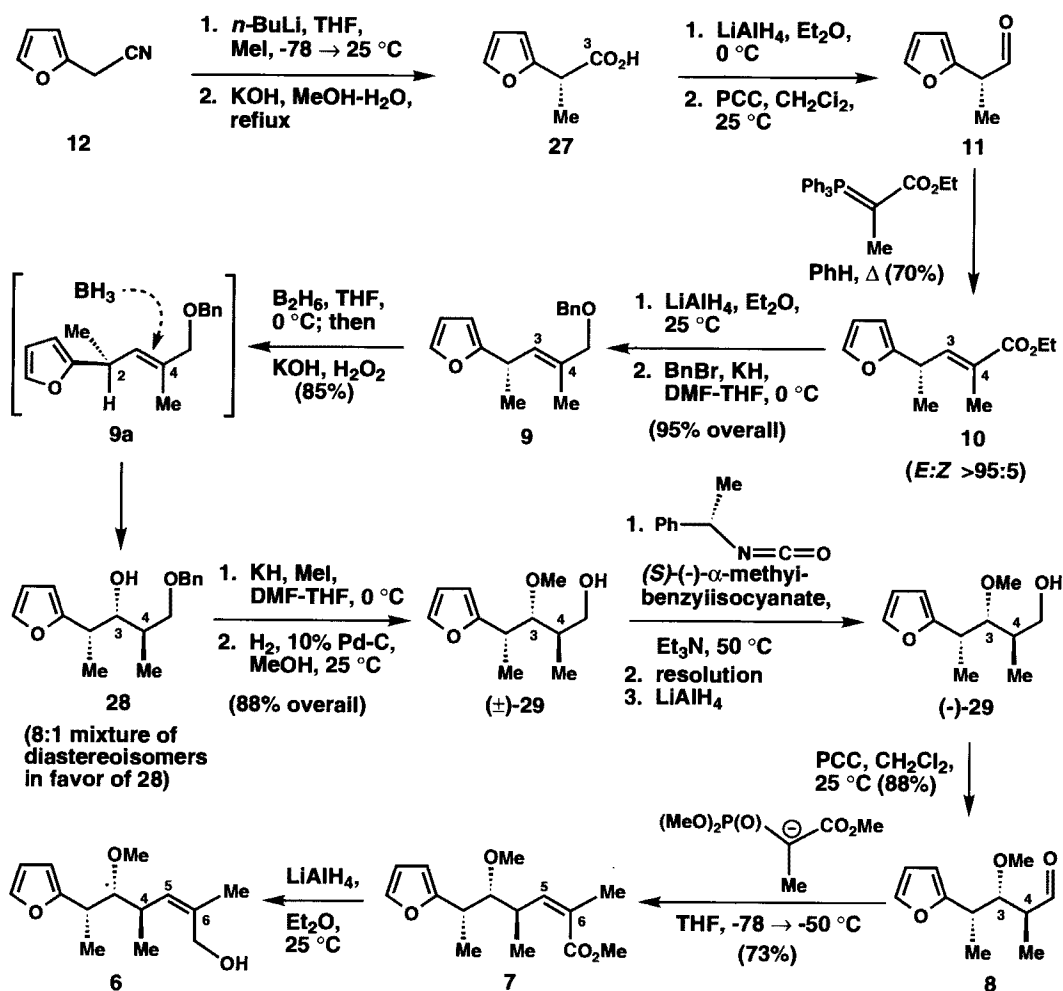
precursor of **22**. In the synthetic direction, treatment of allylic alcohol **24** with triethyl orthoacetate and an acid catalyst would be expected to afford mixed ketene acetal **23** as a transitory intermediate. Once formed, **23** would participate in a [3,3] sigmatropic rearrangement, a Claisen rearrangement, to give γ,δ -unsaturated ester **22**. It is important to note here that the *trans* $\Delta^{16,17}$ double bond geometry in **22** would arise naturally from a chairlike transition state geometry for the sigmatropic event. The Claisen rearrangement and its many variants are, in fact, among the most reliable methods for the construction of *trans* di- and trisubstituted alkenes.³¹

The synthetic problem has now been substantially simplified. Retrosynthetic cleavage of the indicated carbon-carbon bond in **24** provides aldehyde **25** as a potential precursor. A simple carbonyl addition reaction could bring about the conversion of the latter substance to the former. Compound **25** could, in turn, be fashioned in a few straightforward steps from prochiral diol **26**.

12.3 Total Synthesis

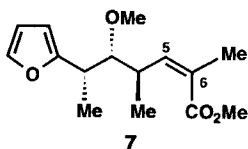
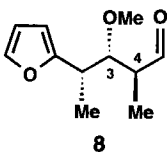
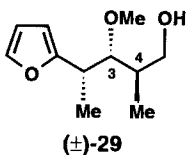
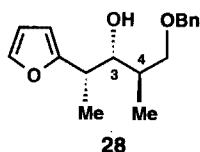
The stereocontrolled synthesis Kishi *et al.* designed for monensin's left wing, intermediate **3**, is detailed in Schemes 2 and 3. 2-Furyl-acetonitrile (**12**), a known substance, can be conveniently converted to 2-(2-furyl)propionaldehyde (**11**) in four straightforward steps. Thus, methylation of the nitrile-stabilized anion derived from **12**, followed by basic hydrolysis of the nitrile function, provides carboxylic acid **27**. Although the (*R*) enantiomer of **27** is illustrated in Scheme 2, this substance is produced in racemic form. From **27**, the synthesis of **11** simply requires adjustment of the oxidation state at C-3. To this end, complete reduction of the carboxyl group with lithium aluminum hydride produces a primary alcohol which can subsequently be converted to **11** through oxidation with pyridinium chlorochromate (PCC). As expected, a Wittig reaction²⁸ between aldehyde **11** and the stabilized ylide, (carbethoxyethylidene)triphenylphosphorane, takes place smoothly in refluxing benzene and gives *trans* α,β -unsaturated ester **10** in 70% yield (*E:Z* > 95:5). In the presence of lithium aluminum hydride, the ethoxycarbonyl function undergoes reduction to give a primary allylic alcohol which can be protected subsequently in the form of a benzyl ether (see intermediate **9**).

An important stage in the synthesis has been reached. The reaction processes described thus far have proceeded uneventfully and have culminated in the synthesis of compound **9**. The stage is now set for an evaluation of the first of two hydroboration reactions. Treatment of **9** with diborane in THF, followed by standard alkaline hydrogen peroxide workup, furnishes an 8:1 stereoisomeric mixture of alcohols in favor of **28** (85% total yield). On the basis of some important precedent,³² it is presumed that compound **9** preferen-



Scheme 2. Synthesis of intermediate 6.

tially adopts the eclipsed conformation **9a**. To minimize destabilizing allylic 1,3-strain,²⁷ the C-4 methyl group in **9a** resides in a common plane with the C-2 hydrogen, not with the bulkier methyl or furanyl groups. The hydroboration reaction then takes place across the sterically less hindered α -face to give **28**. The single stereogenic center in **9** imparts facial selectivity to the hydroboration reaction, while the *anti* C3–C4 relative stereorelationship in **28** arises naturally from the *trans* olefin geometry in **9**. This impressive transformation thus proceeds with both relative and internal asymmetric induction.¹⁸ It should be noted here that although this steric model adequately rationalizes the observed stereochemical

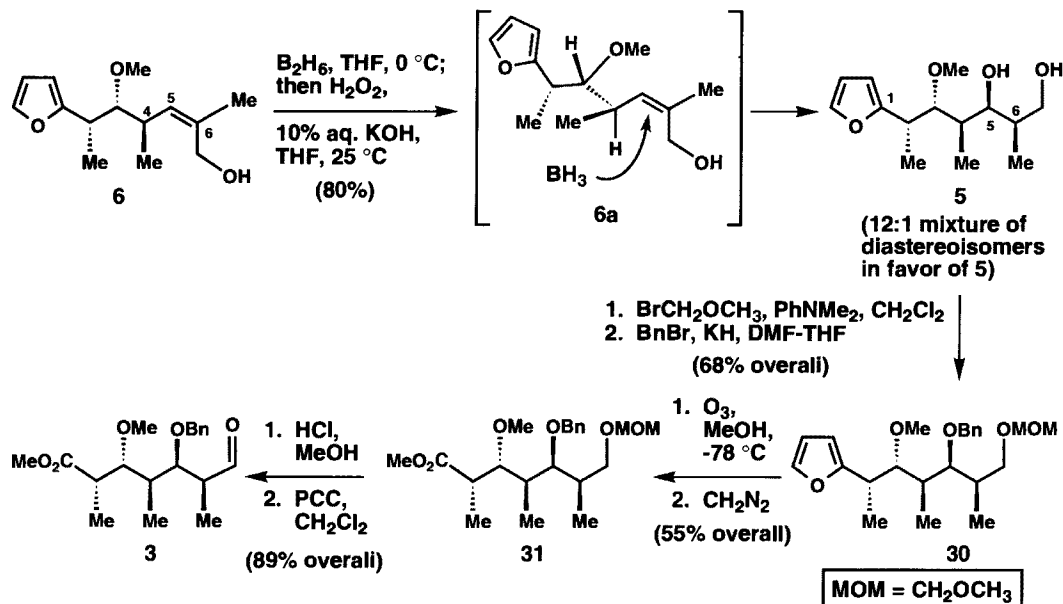


outcome, Houk *et al.* have advanced a modified model in which the Lewis-basic furan oxygen plays an important role by conferring stability (anchimeric assistance) to the transition state leading to the major product **28**.³³

From intermediate **28**, the construction of aldehyde **8** only requires a few straightforward steps. Thus, alkylation of the newly introduced C-3 secondary hydroxyl with methyl iodide, followed by hydrogenolysis of the C-5 benzyl ether, furnishes primary alcohol (±)-**29**. With a free primary hydroxyl group, compound (±)-**29** provides a convenient opportunity for optical resolution at this stage. Indeed, separation of the equimolar mixture of diastereomeric urethanes (carbamates) resulting from the action of (*S*)-(-)- α -methylbenzylisocyanate on (±)-**29**, followed by lithium aluminum hydride reduction of the separated urethanes, provides both enantiomers of **29** in optically active form. Oxidation of the levorotatory alcohol (-)-**29** with PCC furnishes enantiomerically pure aldehyde **8** (88% yield).

Extensive studies of the Wittig and the related Horner–Wadsworth–Emmons reaction have shown that the structural features of the carbonyl component and/or the ylide component, the solvent, and the reaction temperature can all significantly influence the stereochemical outcome of the olefination event.²⁸ Interestingly, when aldehyde **8** is condensed with the stabilized anion derived from (MeO)₂P(O)CH(CH₃)CO₂Me in THF at -78 → -50 °C, *cis* α,β -unsaturated ester **7** is produced in stereoisomerically homogeneous form (73% yield). Reduction of the methoxycarbonyl function in **7** using lithium aluminum hydride then furnishes allylic alcohol **6**, setting the stage for the second hydroboration step. As before, it was anticipated that the conformation around the C4–C5 bond in **6** would be controlled by allylic 1,3-strain (see conformer **6a**, Scheme 3), and that a hydroboration/oxidation of the $\Delta^{5,6}$ double bond would take place regio- and diastereoselectively across the less hindered β -face to give compound **5**. In the event, treatment of **6** with diborane in THF at 0 °C affords, after standard oxidative workup, a 12:1 mixture of diastereoisomers in favor of the desired compound **5** (80% total yield). The C-4 stereocenter in **6** imparts a significant degree of facial selectivity to this hydroboration reaction (1,2-asymmetric induction), and the *syn* C5–C6 stereorelationship in **5** arises stereospecifically from the *Z* olefin geometry in **6** (internal asymmetric induction).

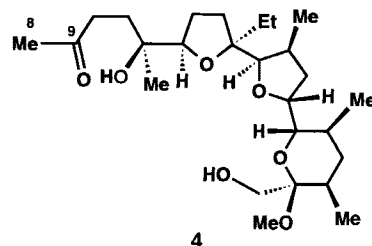
The construction of the five contiguous stereocenters required for a synthesis of compound **3** is now complete; you will note that all of the substituents in compound **5** are positioned correctly with respect to the carbon backbone. From intermediate **5**, the completion of the synthesis of the left-wing sector **3** requires only a few functional group manipulations. Selective protection of the primary hydroxyl group in **5** as the corresponding methoxymethyl (MOM) ether, followed by benzylation of the remaining secondary hydroxyl, provides intermediate **30** in 68% overall yield. It was anticipated all along that the furan nucleus could serve as a stable substi-

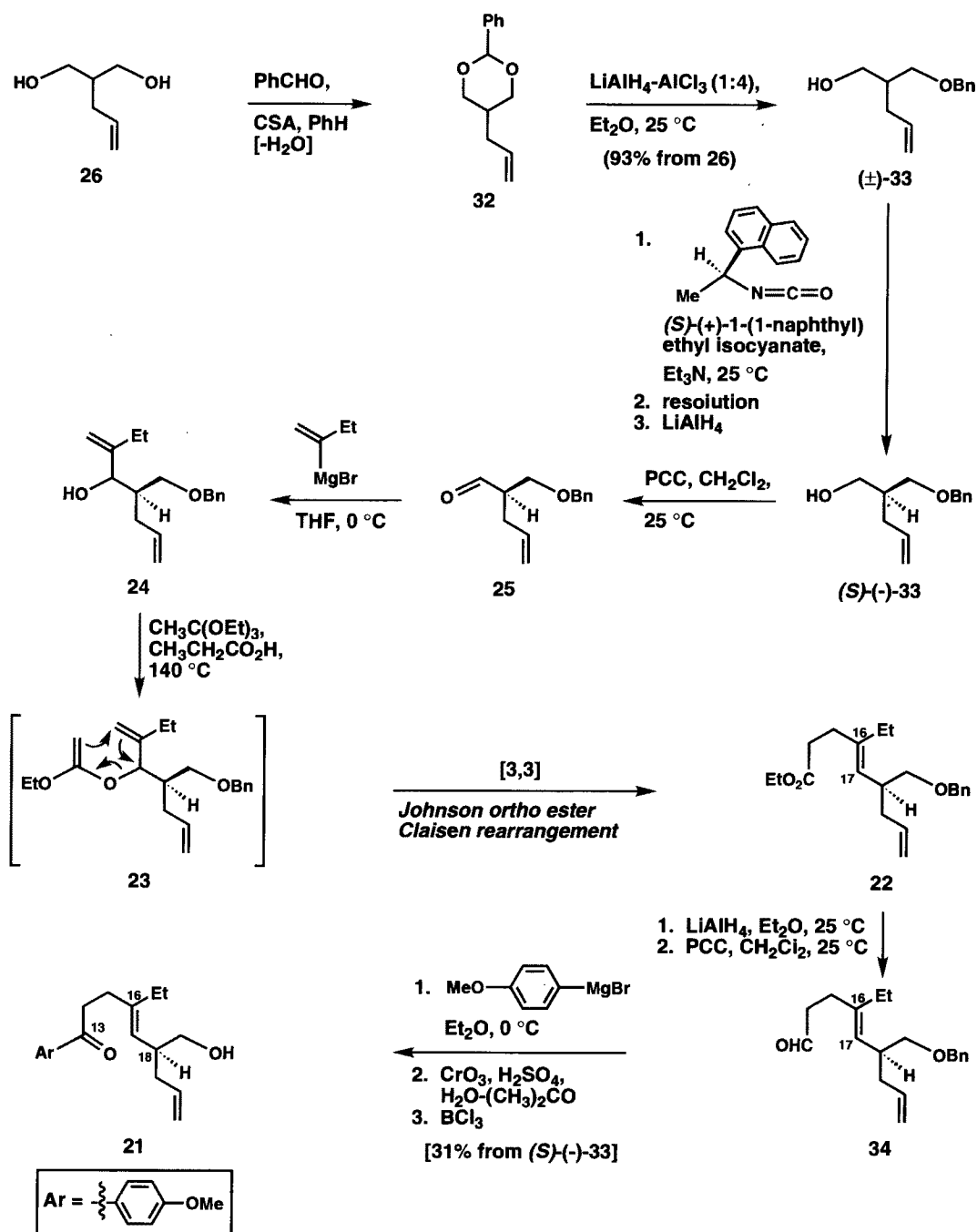


Scheme 3. Synthesis of intermediate **3**.

tute for a carboxyl group.^{25,26} Gratifyingly, the furan ring has been impervious to all of the reactions described thus far, and it has even served as a stereocontrolling group in a crucial transformation (see **9** \rightarrow **28**, Scheme 2). Nonetheless, it is now time to effect the oxidative cleavage of the furan ring. As an electron-rich entity, a furan ring would be expected to react smoothly with an electrophilic oxidant such as ozone. Indeed, exposure of a solution of compound **30** in methanol to ozone at $-78\text{ }^\circ\text{C}$ furnishes a carboxylic acid which undergoes conversion to methyl ester **31** in the presence of diazomethane (55 % overall yield). Subjection of **31** to concentrated HCl in methanol accomplishes the solvolysis of the MOM ether, providing a primary alcohol which can be oxidized to aldehyde **3** with PCC (89 % overall yield).

The synthesis of the right-wing sector, compound **4**, commences with the prochiral diol **26** (see Scheme 4). The latter substance is known and can be conveniently prepared in two steps from diethyl malonate via *C*-allylation, followed by reduction of the two ethoxycarbonyl functions. Exposure of **26** to benzaldehyde and a catalytic amount of camphorsulfonic acid (CSA) under dehydrating conditions accomplishes the simultaneous protection of both hydroxyl groups in the form of a benzylidene acetal (see intermediate **32**, Scheme 4). Interestingly, when benzylidene acetal **32** is treated with lithium aluminum hydride and aluminum trichloride (1:4) in ether at $25\text{ }^\circ\text{C}$, a Lewis acid induced reduction takes place to give





Scheme 4. Synthesis of intermediate 21.

the monobenzyl ether (\pm)-**33** (93 % overall yield from **26**). Compound (\pm)-**33** is a chiral, racemic substance that can be conveniently resolved at this stage. As expected, (\pm)-**33** condenses smoothly with (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate, giving an equimolar mixture of separable diastereomeric urethanes. Lithium aluminum hydride reduction of the separated urethane diastereomers then furnishes the levorotatory and dextrorotatory monobenzyl ethers, (*-*)-**33** and (+)-**33**, respectively. It was found that (*-*)-**33** can be converted in a few steps to (*-*)-2-methylpentanoic acid, the absolute configuration of which is known. The configuration of the stereocenter in (*-*)-**33** is, therefore, assigned as (*S*).

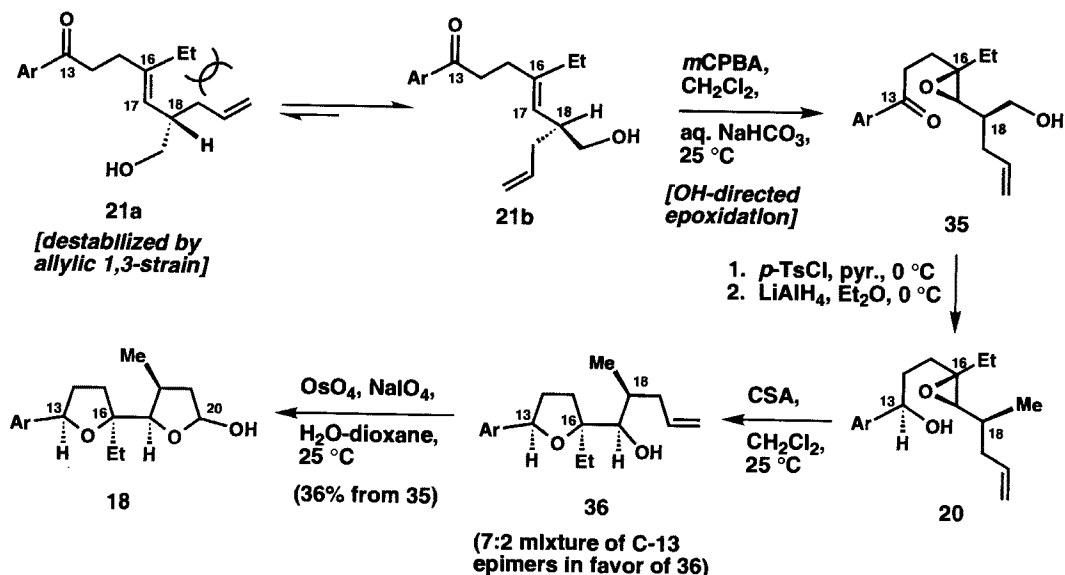
In the presence of PCC, (*-*)-**33** undergoes oxidation to aldehyde **25**. The latter substance is naturally electrophilic, and it combines smoothly with the Grignard reagent derived from 2-bromo-1-butene to give allylic alcohol **24** as a mixture of diastereoisomers. It is, however, of no consequence that **24** is produced as a stereoisomeric mixture because both allylic alcohol diastereomers undergo conversion to the same *trans* γ,δ -unsaturated ester **22** on treatment with triethyl orthoacetate and propanoic acid at 140 °C. The conversion of **24** to **22**, in this manner, constitutes an example of the Johnson ortho ester Claisen rearrangement,³⁰ a most powerful and reliable method for the construction of *trans* alkenes,³¹ and it proceeds through the intermediacy of the mixed ketene acetal **23**. It is important to note that the stereocenter that could not be defined in the carbonyl addition reaction is destroyed during the course of the [3,3] sigmatropic rearrangement.

The homology between **22** and **21** is obviously very close. After lithium aluminum hydride reduction of the ethoxycarbonyl function in **22**, oxidation of the resultant primary alcohol with PCC furnishes aldehyde **34**. Subjection of **34** to sequential carbonyl addition, oxidation, and deprotection reactions then provides ketone **21** (31 % overall yield from (*-*)-**33**). By virtue of its symmetry, the dextrorotatory monobenzyl ether, (*R*)-(+)-**33**, can also be converted to compound **21**, with the same absolute configuration as that derived from (*S*)-(*-*)-**33**, by using a synthetic route that differs only slightly from the one already described.

Although compound **21** contains two potentially oxidizable carbon-carbon double bonds, the $\Delta^{16,17}$ olefin is more electron-rich than the monosubstituted terminal olefin and should, therefore, be more susceptible to oxidation in the presence of an electron-deficient oxidant such as *m*CPBA. Moreover, the tetrasubstituted C16-C17 double bond is closer in space to the free primary hydroxyl group, a function well known for its capacity to direct the course of olefin epoxidations.²⁹ On these grounds, a site-selective, hydroxyl-directed epoxidation of the $\Delta^{16,17}$ double bond would be expected. A hydroxyl-directed *m*CPBA epoxidation of the $\Delta^{16,17}$ double bond would also be expected to be diastereoselective, for compound **21** would preferentially adopt a conformation that minimizes destabilizing allylic 1,3-strain (see conformer **21b**, Scheme 5). In conformer **21b**, the C-16 ethyl group resides in a

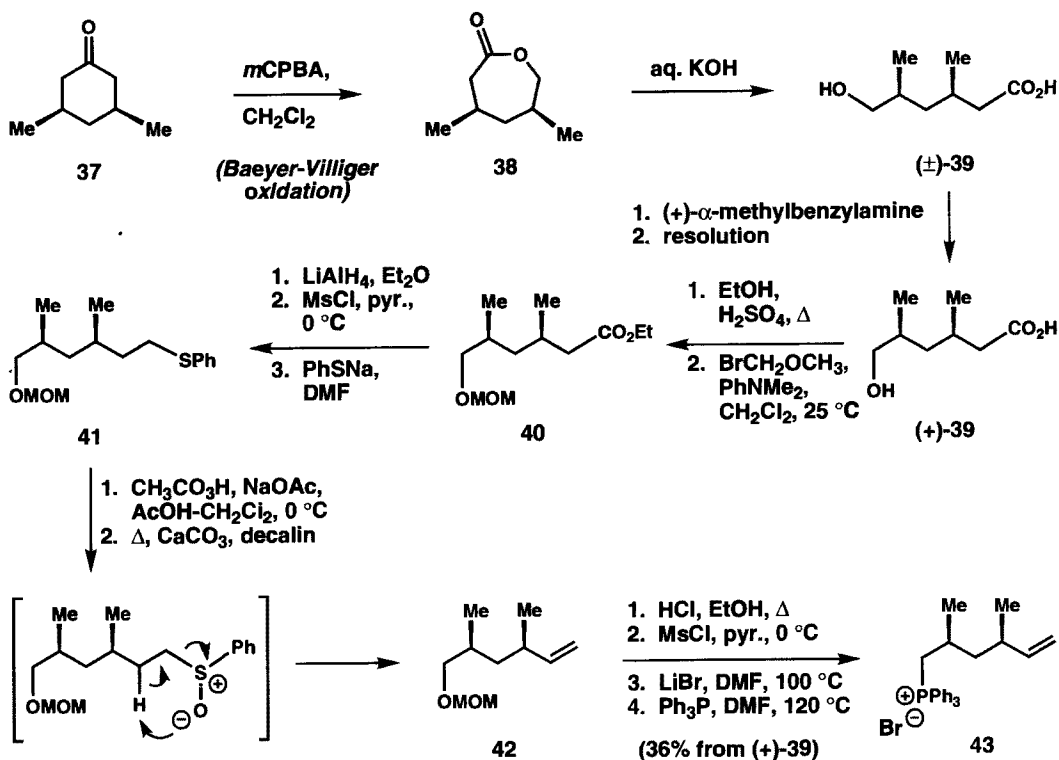
common plane with the smallest substituent attached to C-18, namely hydrogen. The β -oriented hydroxymethyl group could then guide the epoxidation of the β -face of the $\Delta^{16,17}$ double bond. In the event, treatment of a solution of **21** in CH_2Cl_2 /aqueous NaHCO_3 with *m*CPBA at 25°C results in the formation of a single epoxide stereoisomer, compound **35**, in near quantitative yield; you will note that the transition state leading to the epoxidation of the α -face would be significantly destabilized by allylic 1,3-strain.

Although the free primary hydroxyl group in compound **35** has served a most important function in this synthesis, it is not expressed in the natural product, and it must therefore be removed. To this end, treatment of **35** with *para*-toluenesulfonyl chloride and pyridine furnishes a keto sulfonate ester which can be converted to epoxy alcohol **20** in one step on treatment with lithium aluminum hydride. The action of lithium aluminum hydride on the keto sulfonate ester results in the reductive removal of the tosylate function and the reduction of the C-13 keto group. It is interesting to note that the reduction of the ketone is diastereoselective. On treatment with CSA in CH_2Cl_2 , epoxy alcohol **20** participates in an acid-induced 5-*exo* epoxide-opening reaction with inversion of configuration at C-16, giving a separable 7:2 mixture of diastereomeric tetrahydrofurans, epimeric at C-13, in favor of the desired stereoisomer **36**. Oxidative cleavage of the terminal olefin in **36** with osmium tetroxide and sodium periodate then provides lactol **18** (36% overall yield from **35**).

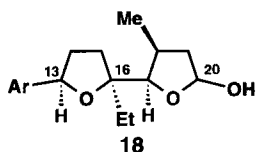


Scheme 5. Synthesis of intermediate **18**.

The synthesis of phosphonium bromide **43**, the immediate precursor of phosphorous ylide **19**, is summarized in Scheme 6. A logical starting material for a synthesis of **42** is achiral *cis*-3,5-dimethylcyclohexanone (**37**) because this compound already contains all of the carbon atoms found in **43**, including the requisite *syn*-1,3-dimethyl system. In the presence of *m*CPBA, **37** participates in a Baeyer–Villiger oxidation,³⁴ giving a ring-expanded seven-membered lactone (see **38**). Basic hydrolysis of the latter substance (**38**) then furnishes the racemic hydroxy acid (\pm)-**39**, which can be resolved by fractional crystallization of the derived (+)- α -methylbenzylamine salt. Subjection of the dextrorotatory hydroxy acid (+)-**39** to a Fischer esterification affords, after protection of the free hydroxyl group as a MOM ether, compound **40**. A complete reduction of the ethoxycarbonyl function in **40** can be achieved with lithium aluminum hydride, and the resulting primary alcohol can be converted, via the intermediacy of the corresponding mesylate, to sulfide **41**. It is, of course, well known that sulfides are rapidly oxidized in the presence of peroxy acids; compound **41** is no exception. Indeed, treatment of **41** with peracetic acid furnishes a sulfoxide which on heating obligingly participates in



Scheme 6. Synthesis of phosphonium bromide **43**.

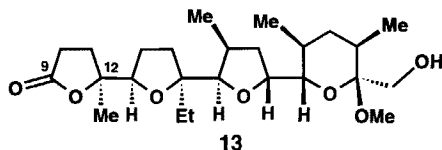


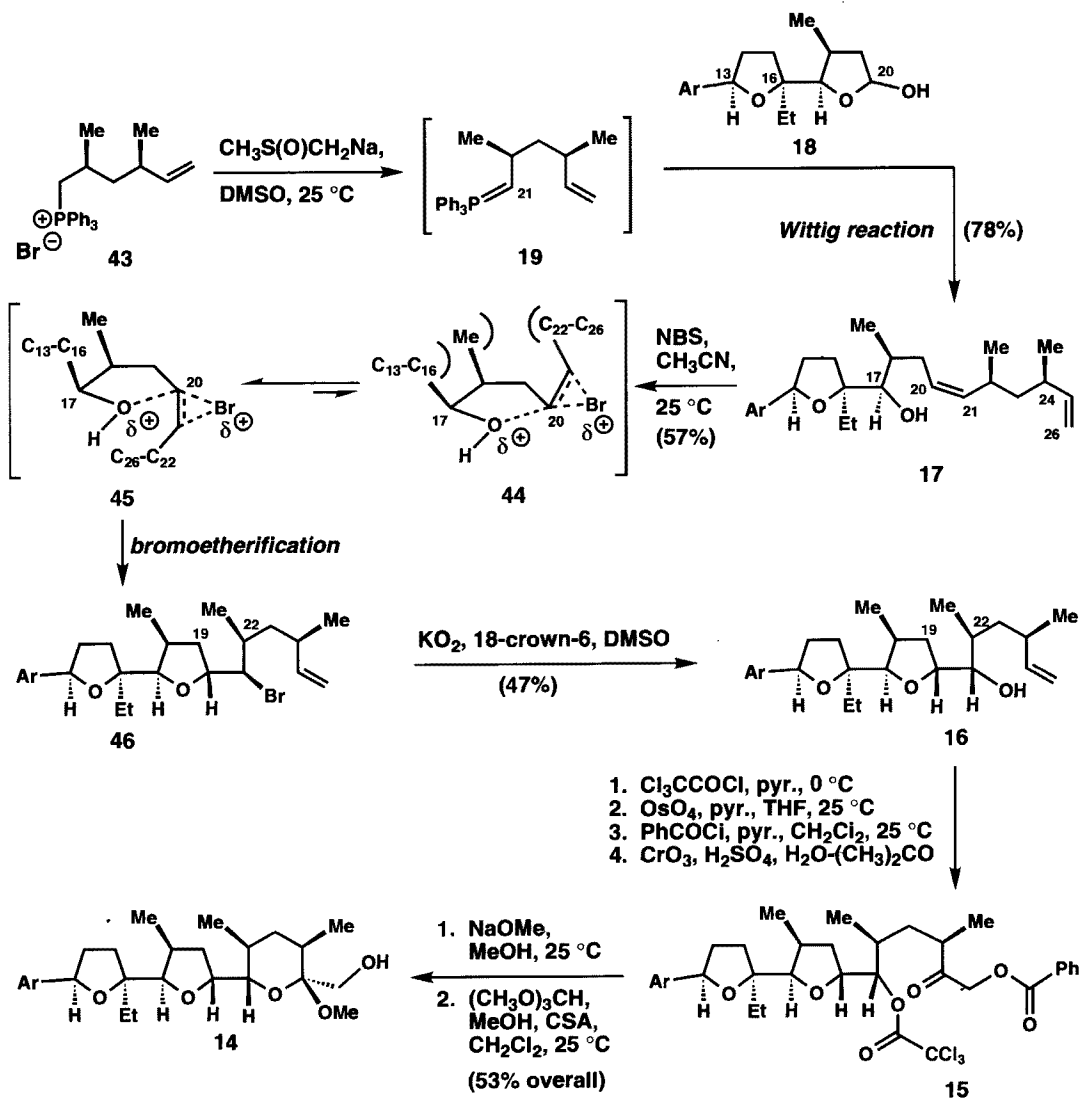
a *syn*-elimination reaction to give **42**. Acid-induced solvolysis of the MOM ether in **42** then provides a primary alcohol which can be transformed to phosphonium bromide **43**, the precursor to ylide **19**, in three straightforward steps (36 % overall yield from (+)-**39**).

It was anticipated that phosphorus ylide **19** could be joined with compound **18**, through a Wittig reaction (Scheme 7). It is important to recognize that lactol **18** is a latent aldehyde; lactol **18** is a participant in a ring-chain tautomeric equilibrium³⁵ with the open-chain hydroxy aldehyde tautomer. Even though this tautomeric equilibrium strongly favors the closed lactol form, the hydroxy aldehyde tautomer is a reactive electrophile and could be intercepted, as it is produced at equilibrium, with a suitable nucleophile. As expected, when phosphorus ylide **19**, generated *in situ* by the action of dimethyl anion ($\text{CH}_3\text{S}(\text{O})\text{CH}_2\text{Na}$) on phosphonium bromide **43**, and lactol **18** are combined in DMSO at 25 °C, a stereoselective Wittig reaction takes place, affording the desired *cis* olefin **17** in 78 % yield together with a small amount (< 2 %) of the stereoisomeric *trans* olefin. The close spatial relationship between the C-17 secondary hydroxyl and the newly introduced site of unsaturation in compound **17** provides a convenient opportunity for the elaboration of the tetrahydrofuran D-ring of monensin. To this end, treatment of bishomoallylic alcohol **17** with *N*-bromosuccinimide (NBS) in acetonitrile furnishes bromide **46** (57 % yield). The action of NBS on **17** diastereoselectively produces a transient bromonium ion which is immediately captured by the proximal hydroxyl group in a manner which is both regioselective and stereospecific. The stereochemical course of this kinetically controlled bromoetherification reaction is consistent with transition state **45**; destabilizing steric interactions in transition state **44** discourage the formation of the alternative diastereomer.

Although the action of electrophilic bromine on **17** effects the desired cyclization reaction, the bromine atom in the product must be replaced by oxygen with inversion of configuration. It was known from the work of Corey *et al.* that superoxide anion can serve as an effective oxygen nucleophile in a variety of contexts.³⁶ When a solution of bromide **46** in DMSO is treated with potassium superoxide (KO_2) and 18-crown-6, the desired $\text{S}_{\text{N}}2$ displacement reaction takes place, giving alcohol **16** in 47 % yield; the success of this transformation is diminished to some extent by competing dehydrobromination reactions. After protection of the newly introduced hydroxyl group as a trichloroacetate ester, sequential dihydroxylation, monobenzylation, and oxidation reactions provide ketone **15**. Cleavage of both ester groupings in **15** using sodium methoxide in methanol is attended by the formation of a single cyclic hemiketal, a substance that undergoes smooth conversion to mixed cyclic ketal **14** on treatment with CSA and trimethyl orthoformate in $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (53 % overall yield from **16**).

It will be recalled that the methoxy-substituted aromatic ring was intended to serve as a stable surrogate for the γ -lactone ring contained within compound **13** (see Scheme 1). This electron-rich aro-





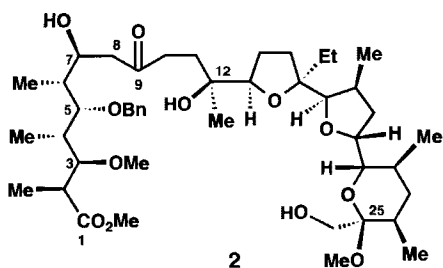
Scheme 7. Synthesis of intermediate 14.

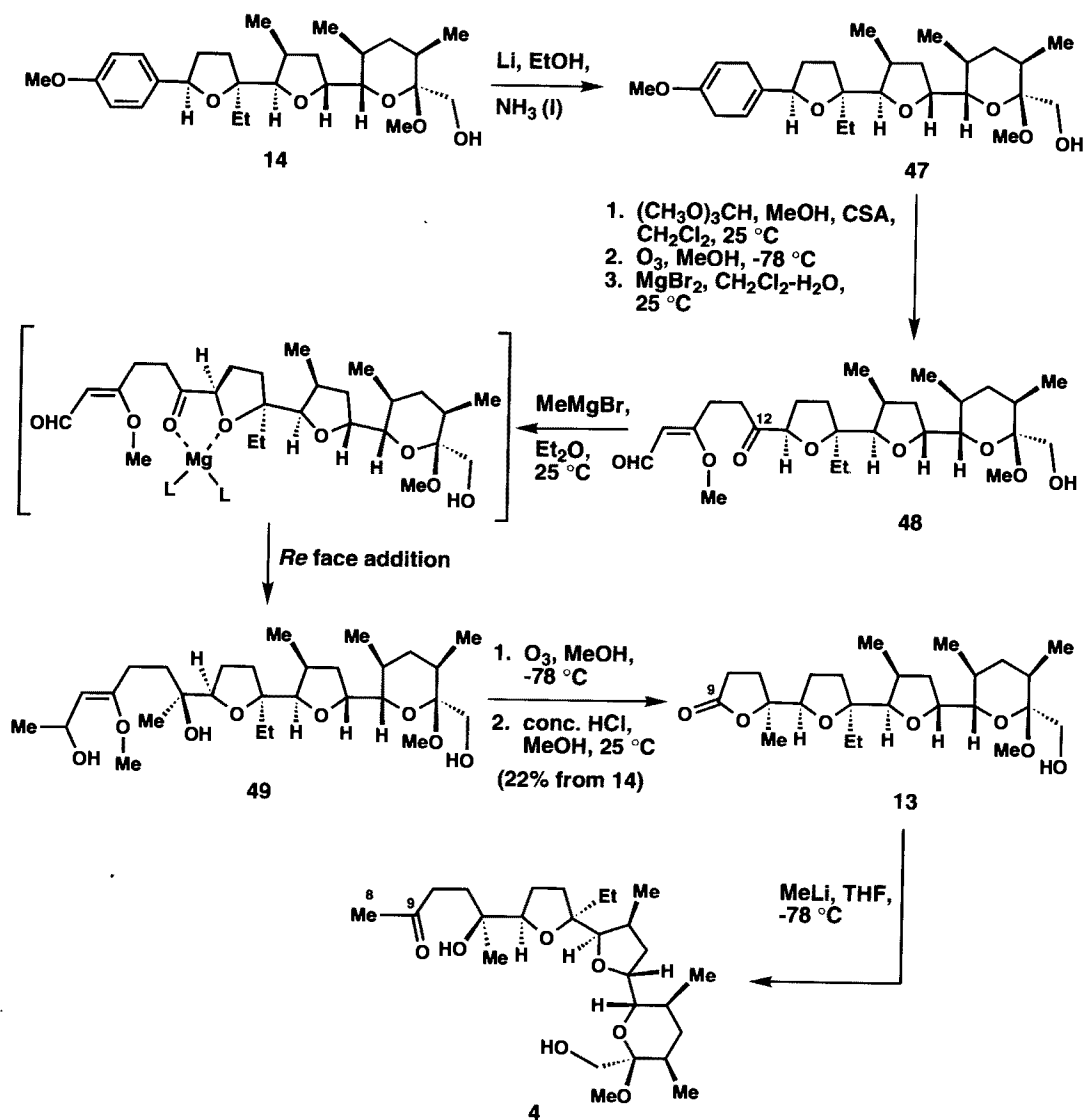
matic nucleus was introduced at an early stage in the synthesis (see **34** \rightarrow **21**, Scheme 4), and it exhibited exceptional stability, withstanding all of the chemical transformations that allowed the assembly of the three contiguous cyclic ether rings of the natural product. Nevertheless, in the presence of lithium metal and ethanol in liquid ammonia, the aromatic ring in compound **14** suffers a Birch reduction,³⁷ and undergoes conversion to methyl enol ether **47** (Scheme 8). Not surprisingly, the methyl enol ether function in compound **47** is transformed to a dimethyl ketal on treatment with acidic methanol. After ozonolytic cleavage of the remaining carbon-carbon double bond, exposure of the resulting ketoaldehyde ketal to magnesium bromide in wet methylene chloride then provides compound **48**.

On the basis of Cram's pioneering studies^{22a,38} and the previous synthesis of lasalocid A by the Kishi group,¹² the C-12 keto function in **48**, situated adjacent to an oxygen-bearing stereocenter, might be expected to undergo a highly diastereoselective, α -chelation-controlled, carbonyl addition reaction in the presence of an appropriate organometallic reagent. Tertiary alcohol **49** is, in fact, produced smoothly, with the desired configuration at C-12, on treatment of **48** with methylmagnesium bromide. The production of **49** is consistent with a chelated transition state in which the nucleophile adds to the less hindered *Re* diastereoface of the ketone. Although it was not reported, the aldehyde carbonyl in **48** presumably reacts with the Grignard reagent as well.

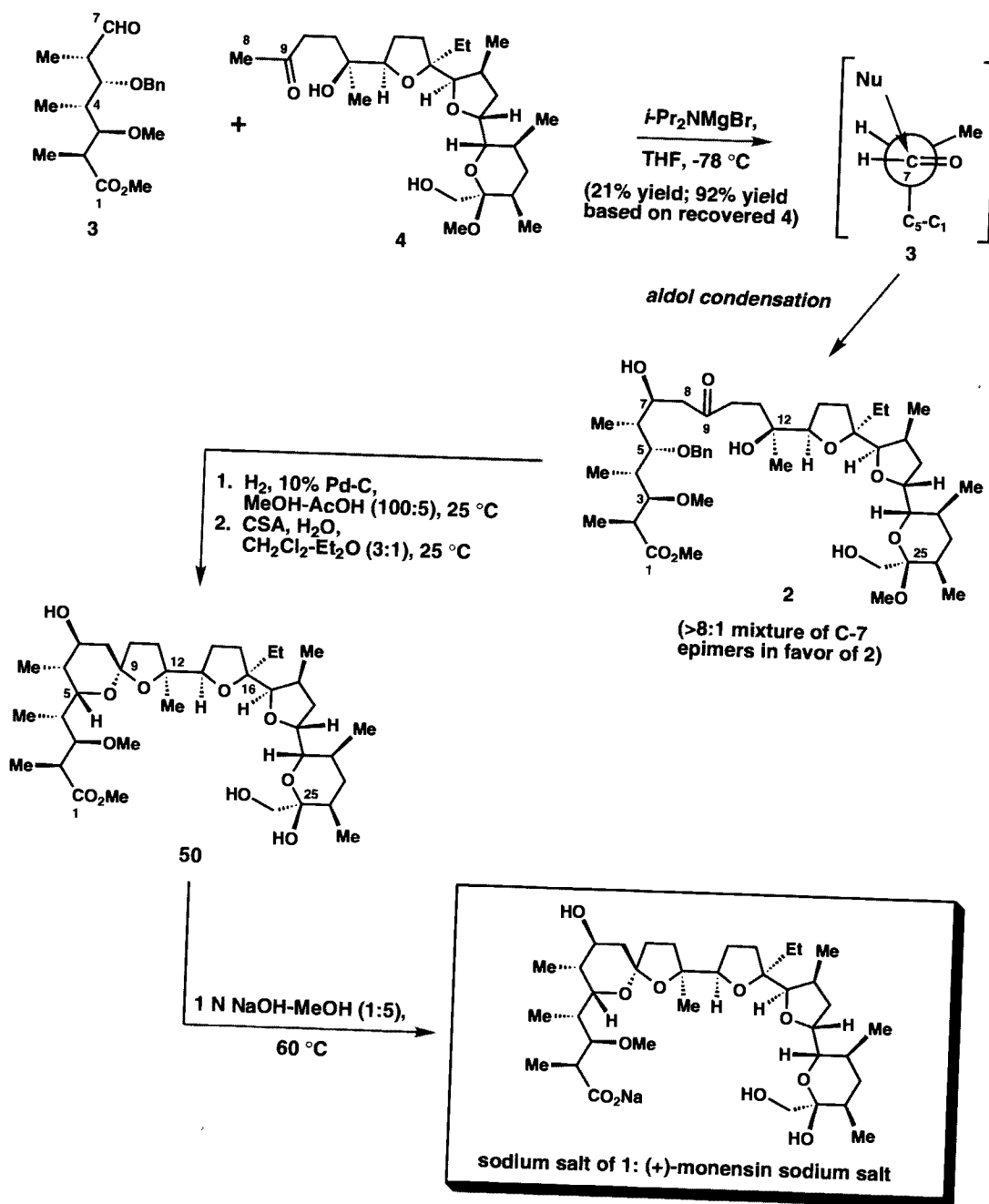
The degradation of the γ -lactone ring surrogate is complete upon oxidative cleavage of the vinyl ether function in **49** with ozone. Exposure of the resulting γ -hydroxy ester to HCl in MeOH at 25 °C then affords γ -lactone **13** (22 % overall yield from **14**). As expected the electrophilic C-9 lactone carbonyl in **13** reacts smoothly with methyllithium, giving methyl ketone **4** after workup in nearly quantitative yield. The synthesis of the right-wing sector of monensin is now complete.

A critical stage in the synthesis of monensin has been reached. Having witnessed the syntheses of key intermediates **3** and **4**, each in optically active form and with the specified absolute configuration, we are now in a position to address their union and the completion of the total synthesis of **1** (Scheme 9). It is instructive to recall that the monensin molecule conceals a potential aldol bond construction (see **1** \rightarrow **2** \rightarrow **3** + **4**, Scheme 1). The convergent union of the left- and right-wing sectors through an aldol reaction, a process that would simultaneously create the C7-C8 bond and the hydroxyl-bearing C-7 stereocenter, is the cornerstone of Kishi's strategy. Observations made during the course of the synthesis of lasalocid A fueled hopes that the crucial aldol coupling of compounds **3** and **4** would furnish the desired C-7 epimer (compound **2**) as the major product. After considerable experimentation, it was found that the addition of bromomagnesium diisopropylamide to a solution of compounds **3** and **4** in THF at -78 °C can bring about the crucial aldol reaction, affording a >8:1 mixture of diastereo-





Scheme 8. Synthesis of intermediate 4.



Scheme 9. Synthesis of (+)-monensin sodium salt (sodium salt of 1).

meric aldol adducts in favor of **2** (21 % yield; 92 % based on consumed ketone **4**). The production of **2** as the major product is consistent with a Cram–Felkin–Anh model.^{22,23} Although the yield for this aldol coupling can be improved by conducting the reaction at higher temperatures, stereoselectivity is compromised. For example, the two aldol diastereomers are formed in a combined yield of 71 % at 0 °C, but the ratio is 1:1.

Aldol adduct **2** possesses all 26 of the backbone carbon atoms of the natural product, including 16 of the requisite 17 stereogenic centers. To complete the synthesis of monensin (**1**) from compound **2**, all that remains is the construction of the 1,6-dioxaspiro[4.5]decane framework and the execution of a few functional group manipulations (Scheme 9). Kishi's approach to the monensin spiroketal problem was guided by the assumption that the configuration at the spirane juncture (C-9) in **1** is that which is thermodynamically most stable. It might, therefore, be possible to construct monensin's spiroketal by intramolecular ketalization of a dihydroxy ketone under equilibrating conditions.^{19,39} Interestingly, when compound **2** is subjected to hydrogenolysis in MeOH–AcOH (100:5) at 25 °C, a mixture of two stereoisomeric spiroketals is formed. When these two isomers are subsequently exposed to a catalytic amount of CSA in wet CH₂Cl₂–Et₂O at 25 °C, equilibration of the labile spiroketal occurs and the more stable compound **50**, the desired compound, is ultimately produced exclusively. You will note that these reaction conditions also bring about the hydrolysis of the mixed-ketal function at C-25. All that remains is the saponification of the C-1 methoxycarbonyl function, a task smoothly accomplished by using 1 N aqueous NaOH in methanol at 60 °C. Kishi's elegant synthesis of monensin is now complete.

12.4 Conclusion

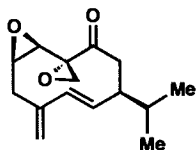
The first total synthesis of the highly oxygenated and stereochemically complex monensin molecule by Kishi *et al.* is one of the great achievements in the area of acyclic stereocontrol. Through careful retrosynthetic analysis, a highly convergent strategy emerged. The adoption of a convergent crossed aldol coupling strategy allowed the complex natural product to be divided into two sectors. Compound **3**, the left-wing sector, possesses only vicinal stereochemical relationships. In **3**, the concatenation of asymmetric carbon atoms encouraged the application of a strategy based on the principle of *stereospecific synthesis by induction* or *stereochemical communication*; under the guiding influence of preexisting stereogenic elements, two hydroboration reactions established four of the five contiguous stereocenters in **3**. By contrast, compound **4**, the right-wing sector, possesses vicinal as well as remote stereorelationships, and its synthesis was achieved through a combination of two fundamentally distinct strategies for controlling stereochemical

relationships – *stereochemical communication* and *stereochemical correlation*. Kishi's elegant synthesis of monensin also provides an instructive demonstration of allylic 1,3-strain as an element for acyclic conformational control. Indeed, allylic 1,3-strain controlled the stereochemical course of several crucial epoxidation reactions.

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1: periplanone B

W. C. Still (1979)

Periplanone B

13.1 Introduction

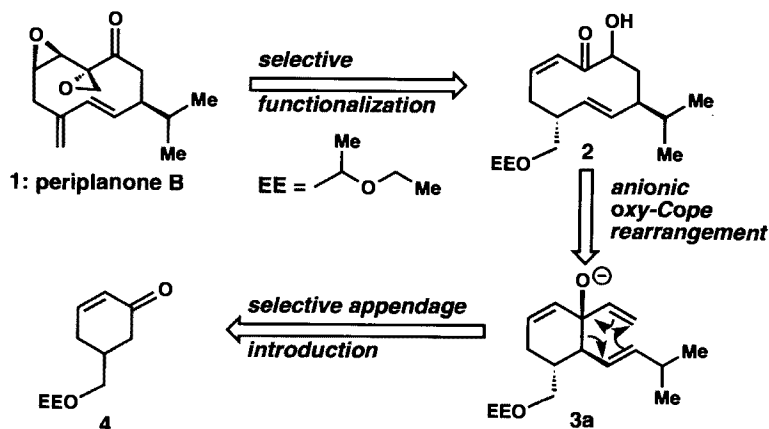
In 1952, it was reported that a constituent of excretions from female American cockroaches of the species *Periplaneta americana* is an extraordinarily potent sex pheromone.¹ Early attempts to isolate and characterize the active compounds were hampered because individual cockroaches store only minute amounts of the pheromone ($\ll 1 \mu\text{g}$), and a full 25 years elapsed before Persoons *et al.* reported the isolation of two extremely active compounds, periplanones A and B.² The latter substance is present in larger relative measure and its germacranoid structure (**1**, without stereochemistry) was tentatively assigned on the basis of spectroscopic data. Thus, in 1976, the constitution of periplanone B was known but there remained a stereochemical problem of a rather serious nature. Roughly three years intervened between the report of the gross structure of periplanone B and the first total synthesis of this substance by W. C. Still at Columbia.³

In the classical era of organic chemistry, before the advent of X-ray crystallographic and sophisticated spectroscopic techniques, an unambiguous synthesis of a natural product played a decisive role in the determination of its structure.⁴ The total synthesis of periplanone B by Still is a rare gem of organic synthesis; its flexibility allowed the preparation of three different diastereoisomers of periplanone B and conclusively established that **1** correctly depicts the gross structure and relative stereochemistry of this molecule.⁵ From the standpoint of strategy and synthetic design, Still's periplanone B synthesis provides a striking demonstration of the power of the anionic oxy-Cope rearrangement for the synthesis of cyclodecanoid frameworks⁶ and, equally noteworthy, it demonstrates how insights

into conformational preferences of ten-membered rings can lead to exceedingly simple and elegant solutions to nontrivial stereochemical problems. In fact, this total synthesis may be regarded as representative of a general strategy in synthesis which exploits conformational properties of medium- or large-sized rings for the purpose of achieving stereochemical control.⁷ This elegant substrate-controlled approach to stereinduction is applicable to the synthesis of both functionalized cyclic and acyclic molecules.

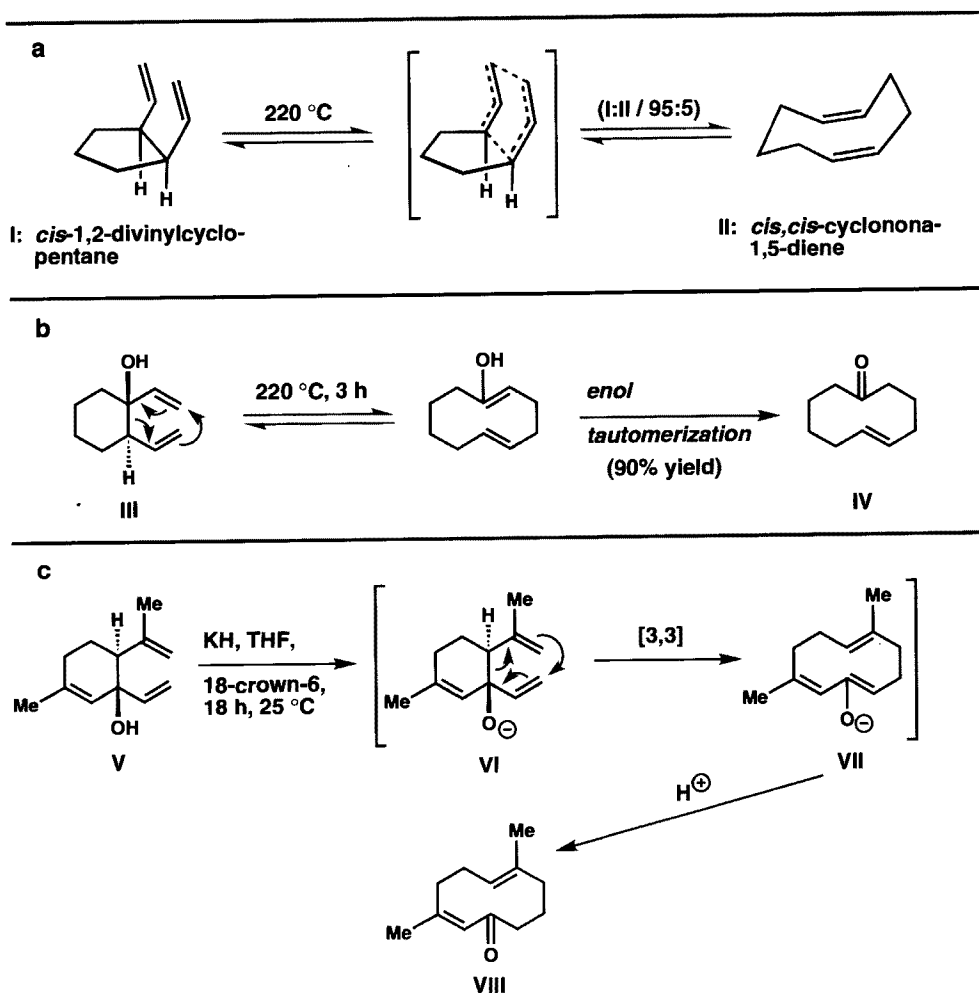
13.2 Retrosynthetic Analysis and Strategy

Since the relative stereochemistry of periplanone B (**1**) was not known at the outset of this synthesis, and an important objective of the synthetic work was to establish the precise structure of the molecule by spectroscopic and bioassay comparisons, it was necessary to design a flexible strategy allowing for the eventual formation of all possible stereoisomers. The logic for Still's design was based on the retrosynthetic analysis shown in Scheme 1. It was anticipated that the epoxides in structure **1** could be stereoselectively and chemoselectively introduced in the final stages, and that the conformation of the epoxide precursor would impose strict control over reaction stereoselectivity. In turn, the conformation of the cyclodecanoid ring would depend heavily on the number of sp^2 centers on its periphery, and thus a provision was made for altering this parameter. With these considerations in mind, functional group manipulations on **1** lead to the cyclodecadienone **2** (racemic). On recognizing the 1-ene-6-one function in the ten-membered ring, one can rapidly identify an anionic oxy-Cope rearrangement⁶ as a potential process for building this system.



Scheme 1. Retrosynthetic analysis of periplanone B (**1**).

The thermal isomerization of a 1,5-diene through a [3,3] sigma-tropic rearrangement is known as the Cope rearrangement;⁸ it is the all-carbon variant of the Claisen rearrangement, and it was first reported in 1940 by A. C. Cope.⁹ Although the Cope rearrangement can accomplish impressive structural transformations in a variety of contexts, its utility in synthesis is, in some cases, diminished by an unfavorable equilibrium between isomeric 1,5-dienes. For example, when *cis*-1,2-divinylcyclopentane (I) is heated to 220 °C, it participates in a [3,3] sigmatropic equilibrium with *cis,cis*-cyclonona-1,5-diene (II) that strongly favors I (I:II / 95:5 at 220 °C)¹⁰ (see Scheme 2a). The preparation of II via Cope rearrangement of I is obviously not a viable option. By contrast, the oxy-Cope rearrange-



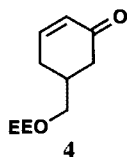
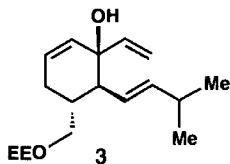
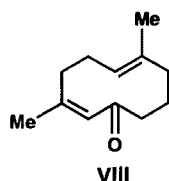
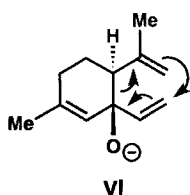
Scheme 2. Representative Cope (a), oxy-Cope (b), and anionic oxy-Cope (c) rearrangements.

ment^{6a,e,8,11} is a particularly valuable tool in synthesis because, in this case, the Cope rearrangement is driven thermodynamically by product isomerization to an unsaturated ketone (see conversion of III to IV, Scheme 2b)¹²; the formation of the carbonyl through enol tautomerization provides a thermodynamic impetus for the oxy-Cope rearrangement and renders the [3,3] sigmatropic process irreversible.

It is important to note that oxy-Cope rearrangements are usually more competent kinetically than Cope rearrangements and can be conducted at lower temperatures. But, nevertheless, the oxy-Cope process can be rendered even more facile simply through deprotonation of the hydroxyl group.¹³ Treatment of oxy-Cope substrate V with potassium hydride and 18-crown-6 (18-C-6) generates alkoxide ion VI which subsequently participates in an irreversible, charge-accelerated anionic oxy-Cope rearrangement to give VIII after protonation of VII¹⁴ (see Scheme 2c). During the course of the conversion of V to VIII, alkoxide ion VI is transformed, through an anionic oxy-Cope rearrangement, into a delocalized (more stable) enolate ion (see VII). Theoretical calculations suggest that the alkoxide in VI could exert a significant effect on the rate of the sigmatropic process by weakening the allylic carbon-carbon bond.¹⁵ It is likely that charge delocalization in the transition state and alkoxide-induced allylic bond cleavage both contribute to the dramatic rate accelerations observed in anionic oxy-Cope rearrangements.

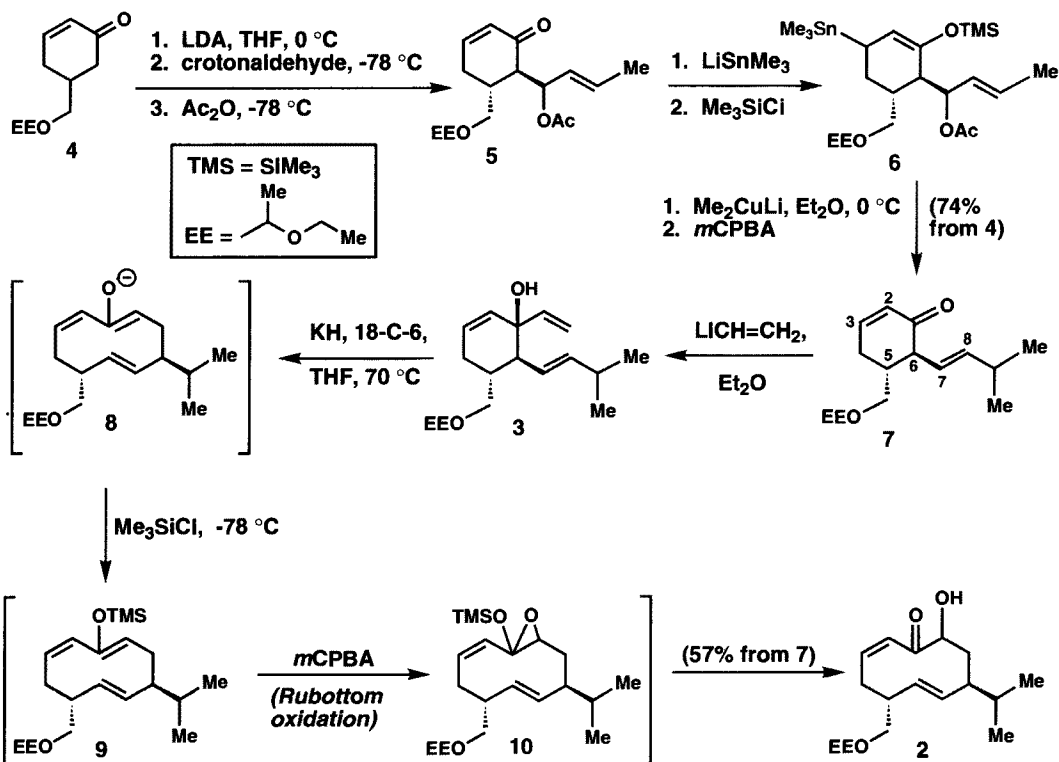
The observation that the oxy-Cope rearrangement can be facilitated by deprotonating the oxy-Cope substrate was first made by D. A. Evans and his group.¹³ Indeed, impressive rate accelerations (e.g. by as much as 10^{17}) can be accomplished simply by converting the oxy-Cope rearrangement substrate into the corresponding alkoxide; the incorporation of a negative charge into the rearrangement array significantly reduces the energy requirements for the [3,3] sigmatropic event.¹⁶ The surprisingly low temperatures at which anionic oxy-Cope rearrangements can be induced are tolerant of a wide variety of organic functional groups, a property which greatly enhances the utility of these reactions for the synthesis of multifunctional organic molecules.

The irreversibility of the anionic oxy-Cope rearrangement and the predictable stereochemical consequences of its highly ordered six-membered transition state geometry (i.e. chair or boat)^{6b,c} make this process ideally suited for the construction of functionalized, unsaturated ten-membered ring ketones. The anionic oxy-Cope rearrangement is among the most reliable processes for the synthesis of functionalized cyclodecanoid frameworks, and, as demonstrated below, served its purpose in Still's periplanone B synthesis admirably. Referring back to Scheme 1, removal of the two unsaturated appendages from intermediate **3a** provides enone **4** as a simple starting material. As we will soon see, this strategy proved superbly suited for the production of the desired target isomers and the solution of the problem at hand.

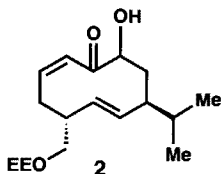
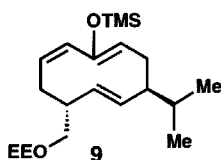
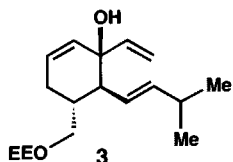
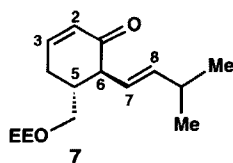


13.3 Total Synthesis

Compound **2** was regarded as a versatile intermediate from which each possible diastereomer of **1** could be assembled. The synthesis of **2** begins with the ethoxyethyl ether (EE) of 5-(hydroxymethyl)-cyclohexenone (**4**, Scheme 3). The first three steps were performed without the isolation of any intermediates. Thus, an aldol reaction between the kinetic lithium enolate derived from **4** and crotonaldehyde furnishes a diastereoisomeric mixture of alcohols which is directly acetylated in the conventional way to give **5**. A conjugate addition of lithium trimethylstannane to the enone function in **5**, followed by trapping of the intermediate enolate with trimethylsilyl chloride, gives intermediate **6**. This form of enone protection is noteworthy since β -stannyl silyl enol ethers are relatively unreactive to most nucleophilic reagents and yet are easily converted back to the starting enone by mild oxidation with *m*CPBA.¹⁷ Treatment of an ethereal solution of **6** with lithium dimethylcuprate induces S_N2' displacement¹⁸ of the allylic acetoxy substituent and furnishes,



Scheme 3. Synthesis of key intermediate **2**.



after an oxidative workup with *m*CPBA, enone **7**. The overall yield of intermediate **7** from **4** is 74 %. A large coupling constant ($J = 10$ Hz) between the two methine protons at C-5 and C-6 is indicative of a diaxial relationship, and a large coupling constant ($J = 16$ Hz) between the vinyl hydrogens at C-7 and C-8 indicates that their relationship is *trans*. A 1,2-addition of vinyl lithium to enone **7** proceeds in a stereoselective fashion to give divinylcyclohexenol **3**. When a solution of **3** in THF is heated to 70 °C in the presence of potassium hydride and 18-crown-6, a smooth anionic oxy-Cope rearrangement⁶ takes place to give the ring-expanded enolate **8**. In this reaction, the active hydrogen in **3** is removed as a proton by KH/18-C-6 and the resultant alkoxide accelerates the oxy-Cope ring expansion process to give **8**.¹³ The solution containing enolate **8** is then cooled to -78 °C and treated with trimethylsilyl chloride to give silyl enol ether **9** which is subjected to a Rubottom oxidation¹⁹ with *m*CPBA to give key intermediate **2** via intermediate **10** in 57 % yield from **7**. Stereochemical assignments for **2** were made on the basis of NMR spectroscopic data and the known preference for a chair-like transition state geometry for the oxy-Cope rearrangement.^{6b,c}

The expedient synthesis of intermediate **2** marked the achievement of the first synthetic objective. The recognition that it should be possible to functionalize the periphery of intermediate **2** in a controlled and selective fashion by taking advantage of conformational preferences of cyclodecanoid intermediates is an elegant and central feature of Still's strategy. To minimize destabilizing transannular interactions, 1,4- and 1,5-cyclodecadienes adopt well-defined and predictable conformations wherein the planes of the olefinic groups and the plane of the ring are perpendicular.^{7a} This conformational preference renders the exterior face of a medium-ring double bond much more accessible and enforces a peripheral attack by reagents (see Figure 1). The synthesis of the first diastereomer of **1** commences with the conversion of the secondary alcohol in **2** to the corresponding *tert*-butyldimethylsilyl ether in the conventional way (see Scheme 4). As expected, the protected C-5 hydroxymethyl substituent in **11** adopts an equatorial orientation preferentially, defines the local conformation^{7e-g} of the ten-membered ring (see structure **11a**), and enforces a stereoselective, peripheral epoxida-

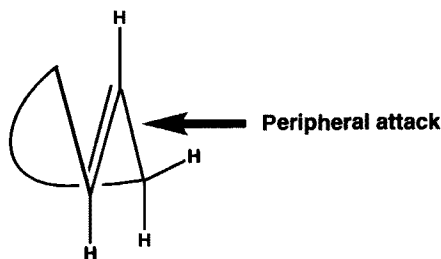
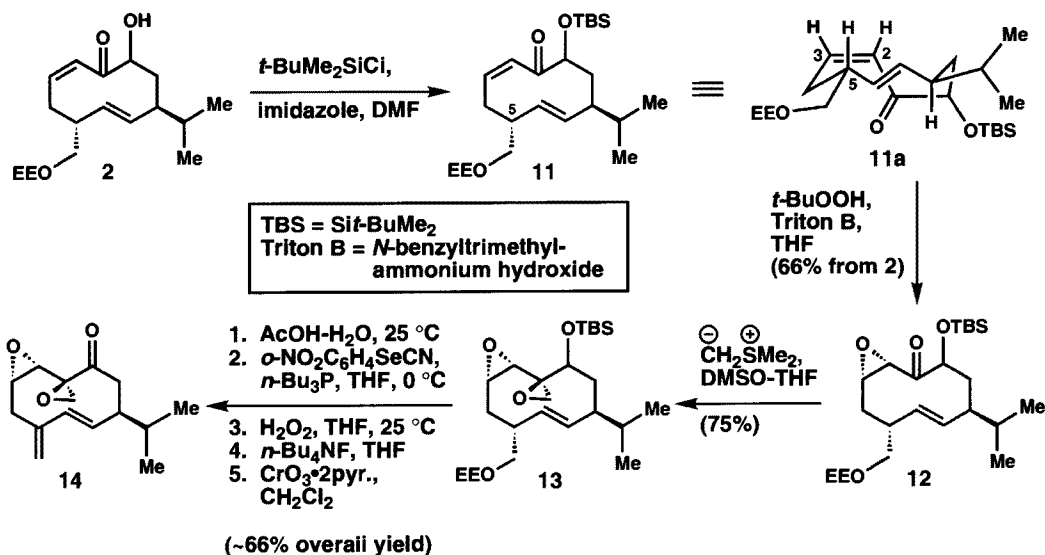


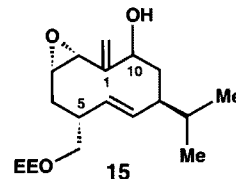
Figure 1. Peripheral attack by external reagents.

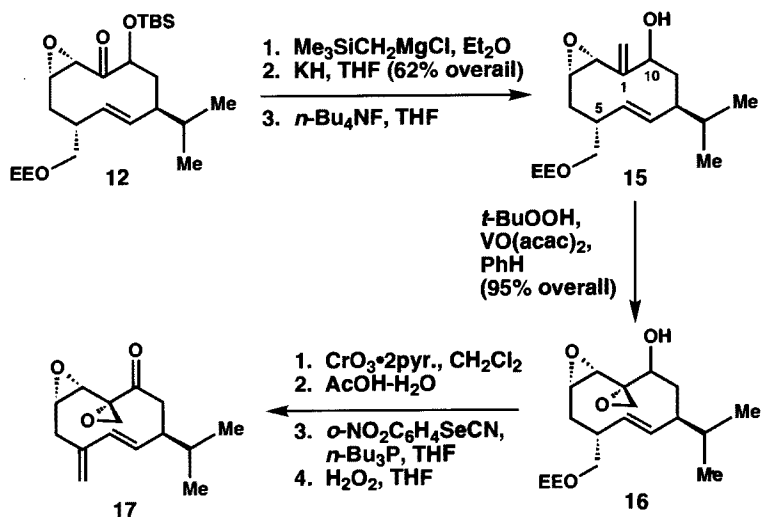


Scheme 4. Synthesis of isomer **14**.

tion of the C2–C3 enone double bond with basic *tert*-butylhydroperoxide²⁰ to give **12**. In the event, *cis*-epoxy ketone **12** is obtained exclusively in 66 % yield from **2**. Ketone **12** adopts a conformation very similar to **11a**, and, in the presence of dimethylsulfonium methylide, the more accessible peripheral ketone diastereoface is attacked in a completely selective manner to give diepoxide **13** (75 % yield) after intramolecular displacement of dimethylsulfide.²¹ Mild acidic hydrolysis of the ethoxyethyl protecting group, followed sequentially by selenenylation,²² selenoxide elimination, desilylation, and Collins oxidation, affords compound **14** (in ca. 66 % overall yield), thereby completing the synthesis of one diastereoisomer of periplanone B. Spectral comparison of this synthetic compound with an authentic sample of periplanone B revealed that the two compounds are non-identical.

In search of the correct isomer of **1**, a second diastereomer was targeted. This compound was prepared from intermediate **12** as described in Scheme 5. Exposure of ketone **12** to trimethylsilylmethylmagnesium chloride gives, after successive treatment with potassium hydride and tetra-*n*-butylammonium fluoride, allylic alcohol **15**. The sequential action of trimethylsilylmethylmagnesium chloride and potassium hydride on **12** gives the exocyclic carbon–carbon double bond²³ (62 % yield) and fluoride treatment accomplishes the removal of the *tert*-butyldimethylsilyl group. Intermediate **15** possesses two sites of unsaturation and the prospects for selectively functionalizing just one may seem grim at first glance. By virtue of the proximal secondary hydroxyl group at C-10, however, the C-1 exocyclic olefin can be regio- and stereo-

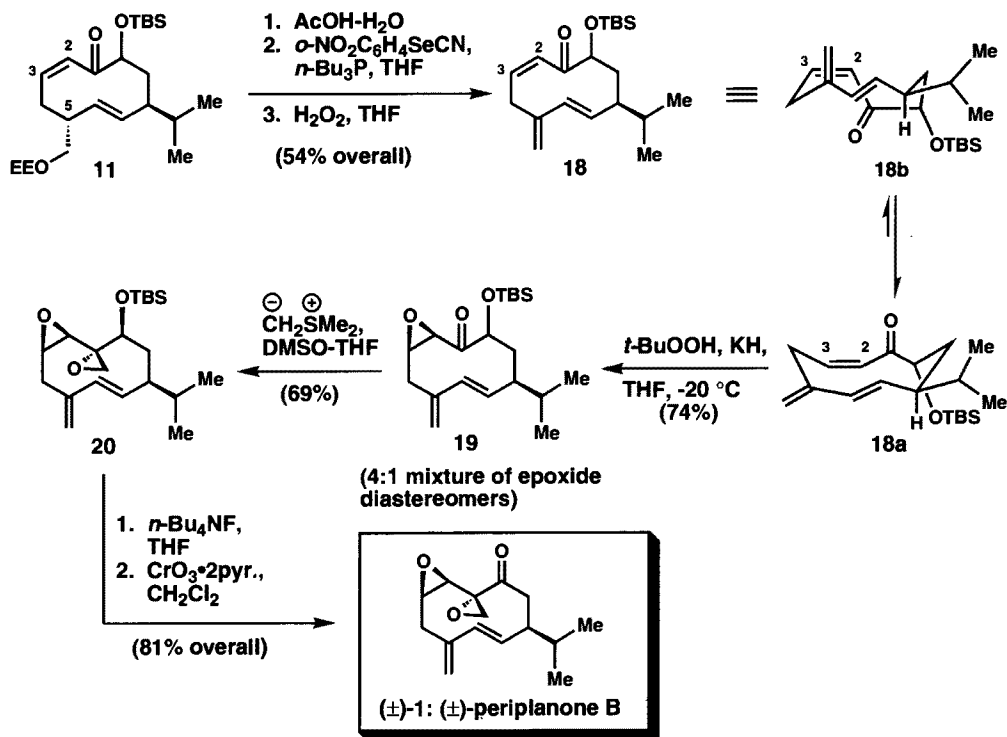




Scheme 5. Synthesis of isomer 17.

selectively functionalized through the application of the Sharpless procedure²⁴ to give epoxy alcohol **16** in 95% yield. The C-10 hydroxyl group directs the oxidation of the C-1 exocyclic olefin.²⁵ Collins oxidation of **16**, followed by reiteration of the same three-step reaction sequence for the construction of the exocyclic methylene at C-5 (as in the synthesis of **14**), furnishes compound **17**, a second diastereomer of **1**. As in the case of isomer **14**, the spectroscopic properties of **17** did not match those of natural periplanone B, and thus the synthesis of a third isomer was undertaken.

In the third sequence, the diastereomer with a β -epoxide at the C2–C3 site was targeted (compound **1**, Scheme 6). As we have seen, intermediate **11** is not a viable starting substrate to achieve this objective because it rests comfortably in a conformation that enforces a peripheral attack by an oxidant to give the undesired C2–C3 epoxide (Scheme 4). If, on the other hand, the exocyclic methylene at C-5 was to be introduced before the oxidation reaction, then given the known preference for an *s-trans* diene conformation, conformer **18a** (Scheme 6) would be more populated at equilibrium. The $\Delta^{2,3}$ olefin diastereoface that is interior and hindered in the context of **18b** is exterior and accessible in **18a**. Subjection of intermediate **11** to the established three-step olefination sequence gives intermediate **18** in 54% overall yield. On the basis of the rationale put forth above, **18** should exist mainly in conformation **18a**. Selective epoxidation of the C2–C3 enone double bond with potassium *tert*-butylperoxide furnishes a 4:1 mixture of diastereomeric epoxides favoring the desired isomer **19**; **19** arises from a peripheral attack on the enone double bond by *tert*-butylperoxide, and it is easily purified by crystallization. A second peripheral attack on the ketone function of **19** by dimethylsulfonium methylide gives intermediate **20** exclusively, in a yield of 69%.



Scheme 6. Synthesis of (±)-periplanone B [(±)-1].

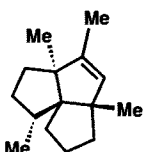
Desilylation of **20**, followed by oxidation of the secondary hydroxyl group furnishes racemic **1** in a yield of 81 %. Spectroscopic and bioassay characteristics of synthetic (±)-**1** matched natural periplanone B in every detail. The constitution and relative stereochemistry of the elusive American cockroach sex excitant periplanone B (**1**) has been secured in a very elegant way.⁵

13.4 Conclusion

In this beautiful synthesis of periplanone B, Still demonstrated a classical aspect and use of total synthesis – the unambiguous establishment of the structure of a natural product. More impressively, he demonstrated the usefulness of the anionic oxy-Cope rearrangement in the construction of ten-membered rings and the feasibility of exploiting conformational preferences of these medium-sized rings to direct the stereochemical course of chemical reactions on such templates.

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1: isocomene

M. C. Pirrung (1979)

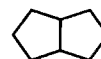
Isocomene

14.1 Introduction

One of the constituents of the rayless golden rod, *Isocoma wrightii*, is the novel tricyclic sesquiterpene isocomene (**1**). Its structure was first revealed in 1977 by Zalkow and coworkers¹ and is distinguished by an angular fusion of three cyclopentane rings (angular triquinane). For a molecule that possesses only fifteen carbon atoms, isocomene is very interesting. Its compact molecular framework is the host of four contiguous stereogenic centers, and the situation is complicated further by the fact that three of these are fully substituted (i.e. quaternary). The expedient and elegant total synthesis of isocomene (**1**) by Michael C. Pirrung² demonstrates, in a dramatic way, the value of intramolecular [2+2] photocycloaddition³ and cation-induced skeletal rearrangement processes for the synthesis of stereochemically and architecturally complex polycyclic molecules.

14.2 Retrosynthetic Analysis and Strategy

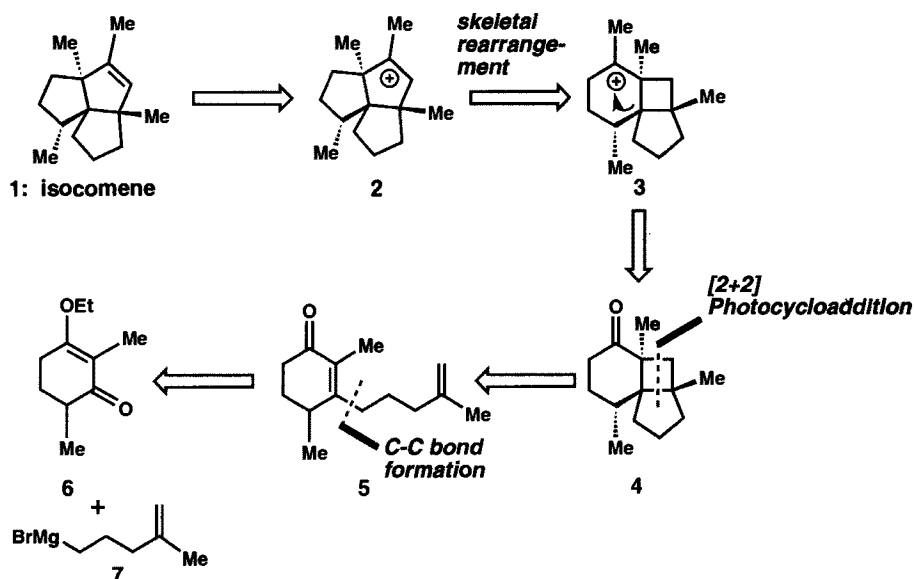
The key features of Pirrung's synthesis of isocomene are outlined retrosynthetically in Scheme 1. Working one step back from **1** gives the tertiary carbocation intermediate **2**. The intermediacy of **2** should be brief, for it should readily participate in an E₁-type reaction, in the forward sense, to give isocomene (**1**). Inspired by the observation that bicyclo[3.3.0] frameworks can be accessed from bicyclo[4.2.0] frameworks through cyclobutyl carbiny cation rear-



bicyclo[3.3.0] system



bicyclo[4.2.0] system



Scheme 1. Retrosynthetic analysis of isocomene (1).

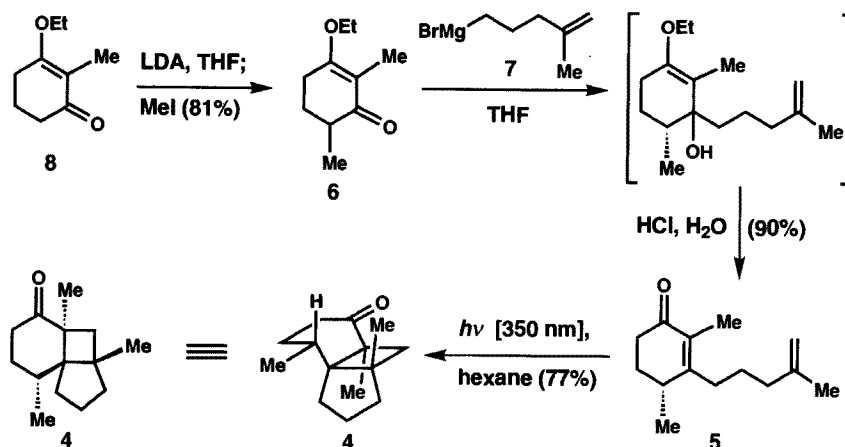
rangements,⁴ it was anticipated that intermediate cation **2** would form upon rearrangement of the isomeric tertiary cation, intermediate **3**. Like intermediate **2**, cation **3** is expected to be a transient species; once formed, its carbon skeleton could rearrange in the indicated way to give **2**. In the context of bicyclo[4.2.0] frameworks, the facility with which cyclobutyl carbanyl cations rearrange to isomeric bicyclo[3.3.0] frameworks was known.⁴ This skeletal rearrangement benefits from the thermodynamic driving force provided by the relief of ring strain inherent in the cyclobutane system.

It was projected that intermediate **3** could be derived in a straightforward manner from ketone **4**. Retrosynthetic dissection of **4** by cleavage of the indicated carbon–carbon bonds leads to intermediate **5**. It is here, in this retrosynthetic step, that we witness significant structural simplification. In the synthetic direction, enone olefin **5** could participate in a photo-induced intramolecular enone–olefin [2+2] cycloaddition reaction to give intermediate **4**. If successful, this single transformation would create two new carbon–carbon bonds and three contiguous, quaternary stereogenic centers⁵ and, from intermediate **4**, the completion of the synthesis would require only two operations. Cleavage of the indicated bond in **5** leads back to simple and readily available starting materials **6** and **7**.

14.3 Total Synthesis

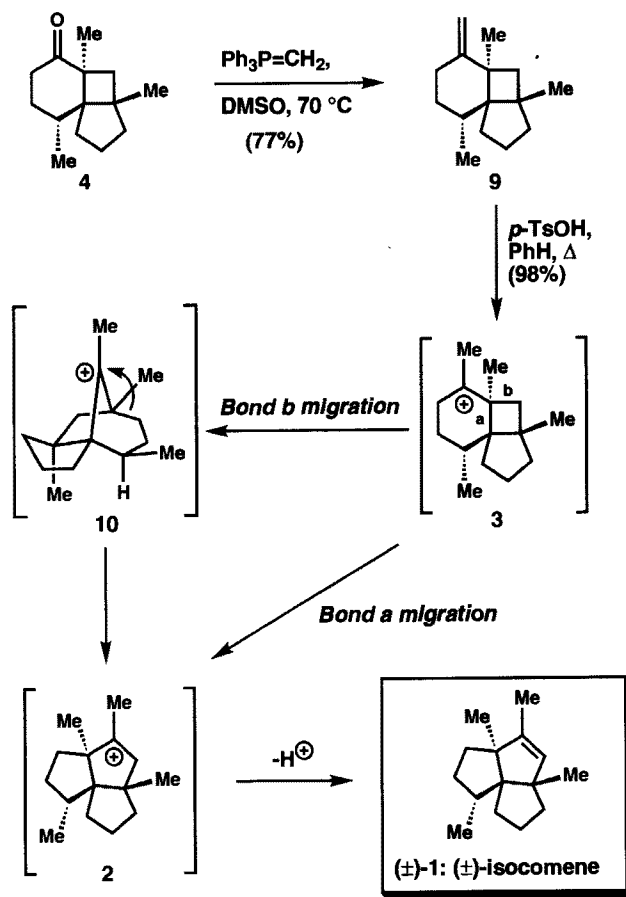
The synthesis of key intermediate **4** is presented in Scheme 2. The synthesis commences with the C-methylation of vinylogous ester **8** to give intermediate **6**. In the presence of Grignard reagent **7**, derived from 5-bromo-2-methyl-1-pentene, the ketone carbonyl in **6** undergoes ready attack to give a labile tertiary alcohol. Enone **5** is obtained in a yield of 90 % when this alcohol is exposed to aqueous HCl. The preparation of intermediate **5** sets the stage for the crucial enone-olefin [2+2] photocycloaddition reaction. In the event, irradiation of a 0.01 M solution of **5** in hexane with light (350 nm) induces a regio- and stereospecific intramolecular [2+2] cycloaddition reaction to give key intermediate **4**. To avoid destabilizing steric interactions, the disubstituted, terminal olefin engages the enone diastereoface opposite to the secondary methyl substituent, and it is noteworthy that photo adduct **4** is produced in 77 % yield. This reaction creates, in one step, a tricyclo[6.3.0.0^{1,6}] undecanone framework and three contiguous stereocenters all of which are quaternary! Single-crystal X-ray analysis of a derivative of **4** established its relative stereochemistry.

It was predicted, *a priori*, that isocomene could be formed simply by treating **4** with methyllithium, followed by exposure of the resultant tertiary carbinol to acid.^{2b} However, many attempts to effect the addition of a variety of nucleophilic methyl derivatives to ketone **4** were unsuccessful. It was revealed by deuterium quenching experiments that ketone **4** undergoes ready enolization in the presence of nucleophilic methyl derivatives. Despite its hindered nature, however, the ketone carbonyl in **4** reacts with methylenetri-



Scheme 2. Synthesis of intermediate **4**.

phenylphosphorane (see Scheme 3). In DMSO at 70 °C, **4** is converted to intermediate **9** through a Wittig reaction.⁶ When **9** is dissolved in benzene and heated to reflux in the presence of *para*-toluenesulfonic acid, the newly formed exocyclic methylene is protonated to give the putative tertiary cation **3**. The carbocation in **3** could conceivably react in several different ways; however, by virtue of its spatial relationship to the cyclobutane ring, the prerequisites for a thermodynamically driven skeletal rearrangement are satisfied. If bond *a* migrates, the isomeric tertiary cation **2** is formed. Loss of a proton from **2** would then complete the synthesis of isocomene (**1**). If, on the other hand, bond *b* in intermediate **3** migrates, then bridged tertiary cation **10** is formed. Although the homology with isocomyl cation **2** is not obvious, intermediate **10** can be converted into **2** after a second bond migration. Thus, either or both rearrangement pathways can lead to the formation of isoco-



Scheme 3. Synthesis of (±)-isocomene [(±)-**1**].

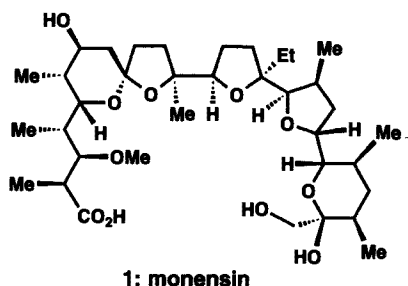
myl cation **2** and thence isocomene. The action of *para*-toluenesulfonic acid on intermediate **9** furnishes racemic isocomene [(±)-**1**] in a most elegant way and in a yield of 98 %!

14.4 Conclusion

In this synthesis, we have witnessed the dramatic productivity of the intramolecular enone–olefin [2+2] photocycloaddition reaction. This single reaction creates three contiguous and fully substituted stereocenters and a strained four-membered ring that eventually provides the driving force for a skeletal rearrangement to give isocomene.

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W. C. Still (1980)

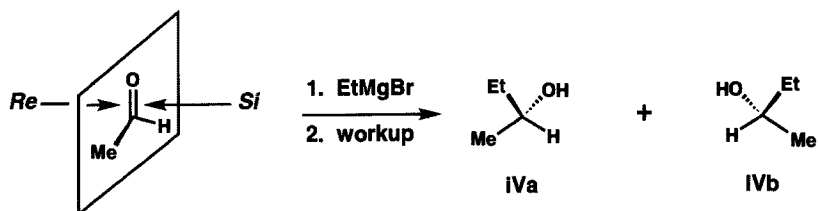
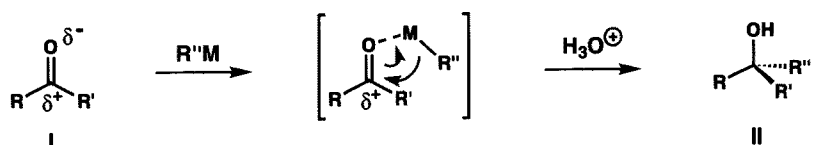
Monensin

15.1 Introduction

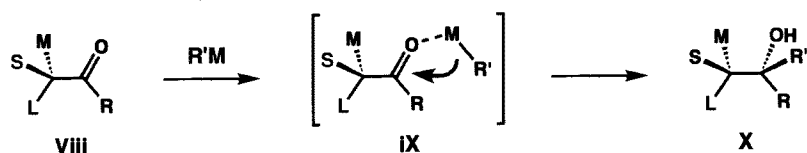
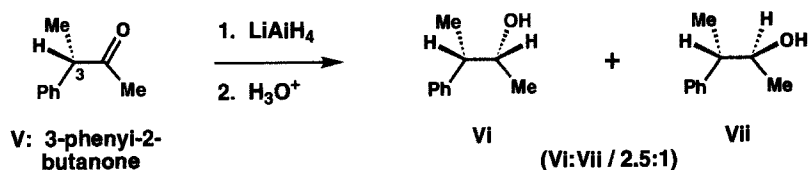
The addition of a carbon nucleophile to a carbonyl group constitutes one of the most powerful and reliable methods for carbon-carbon bond formation known in organic chemistry. The basis for this effective process is the inherent polarization of the carbonyl group. The more electronegative carbonyl oxygen atom withdraws electron density away from the carbonyl carbon, thereby rendering it susceptible to attack by a nucleophile. In a reaction of a carbonyl-containing compound with an organometallic reagent (see I→II, Scheme 1), complexation between the metal counterion and the Lewis-basic carbonyl oxygen atom precedes the carbon-carbon bond forming event. Complexation enhances the electron-deficient character of the carbonyl carbon, and is an important feature of this type of reaction.

In reactions of Grignard reagents with ketones, the simplicity of the overall process (i.e. ketone → tertiary alcohol product) belies the complexity of the mechanistic pathways involved.¹ Grignard reagents form complex mixtures in solution. While some carbonyl addition reactions proceed via a conventional ionic mechanism involving the attack of the Grignard reagent on a precomplexed carbonyl group, others are more consistent with an electron-transfer mechanism. The contributions of E. C. Ashby and others¹ have shown that the important question as to which mechanistic pathway (i.e. ionic or electron transfer) is operative in a particular instance depends on the nature of the ketone, the R group in the Grignard reagent, the purity of the magnesium metal, and the solvent.

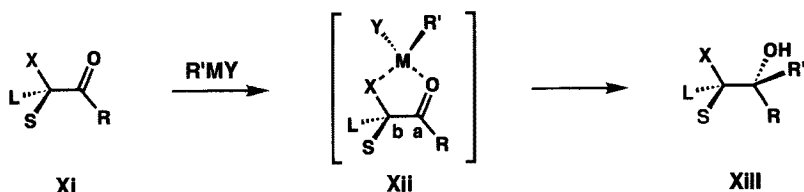
Mechanistic issues notwithstanding, the addition of a carbon nucleophile to the carbonyl group of an aldehyde or a ketone can



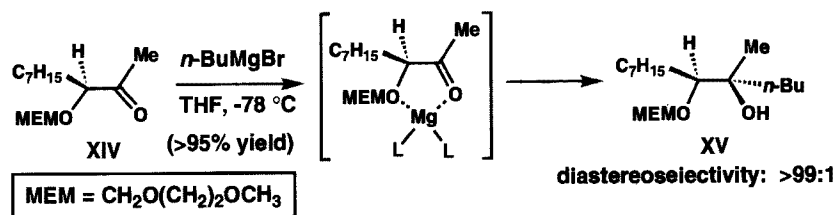
iii: acetaldehyde



$\text{L} > \text{M} > \text{S}$
in order of decreasing
steric bulk

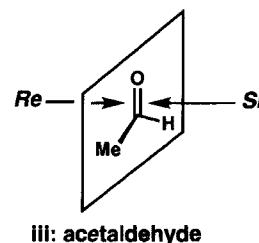


X = heteroatom function
L = large substituent
S = small substituent



Scheme 1. Representative carbonyl addition reactions.

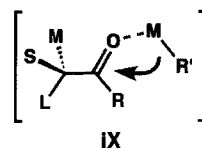
accomplish the formation of a new center of chirality. For example, the action of ethylmagnesium bromide on acetaldehyde (III) produces, after aqueous workup, a racemic mixture of secondary alcohols IVa and IVb (see Scheme 1). A new stereocenter is introduced in this reaction, and the secondary alcohol product is furnished in racemic form because the *Re* and *Si* enantiotopic faces of the carbonyl group of acetaldehyde are equally vulnerable to attack by the Grignard reagent.

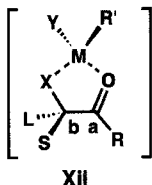


The situation becomes more complicated when one considers the addition of an organic nucleophile to an aldehyde or a ketone that contains a stereocenter in the α position. For example, by virtue of the stereocenter at C-3 in 3-phenyl-2-butanone (V), the two faces of the ketone carbonyl are diastereotopic. As a result, the energy barrier associated with a nucleophilic addition to one diastereoface will be larger than that for addition to the other diastereoface, and unequal amounts of products will be formed. Indeed, treatment of V with lithium aluminum hydride, followed by an aqueous workup furnishes a 2.5:1 mixture of diastereomeric alcohols VI and VII. This particular example has historical significance because it was included in Cram's seminal 1952 paper which offered the following postulate, now known as Cram's rule:² "In non-catalytic reactions of this type, that diastereomer will predominate which would be formed by the approach of the entering group from the *least hindered side* of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric center."

The conversion of VIII to X shown in Scheme 1 illustrates Cram's open-chain model. Cram reasoned that nucleophiles such as Grignard reagents and lithium aluminum hydride probably coordinate with the carbonyl group of the substrate as well as with solvent. As a result, the coordinated carbonyl oxygen becomes the most sterically encumbered group and tends to orient itself between the two least bulky groups attached to the vicinal stereocenter.³ The nucleophile then adds to the more accessible carbonyl diastereoface. Although Cram's open-chain model clearly recognizes the importance of carbonyl complexation and correctly predicts the preferred stereochemical course of many carbonyl addition reactions, the premise that the addition reaction proceeds through a conformation analogous to IX is questionable.⁴ Nonetheless, Cram's pioneering contribution in 1952 provided the inspiration for the important subsequent studies of Cornforth,⁵ Karabatsos,⁶ Felkin,⁷ and Anh.⁸ Cram's rule has contributed greatly to the maturation of our understanding of 1,2-acyclic stereinduction.⁴

In his original paper,² Cram disclosed an alternative model that rationalizes the preferred stereochemical course of nucleophilic additions to chiral carbonyl compounds containing an α heteroatom that is capable of forming a complex with the organometallic reagent. This model, known as the *Cram cyclic* or *Cram chelate model*, has been extensively studied by Cram⁹ and by others,^{4,10}





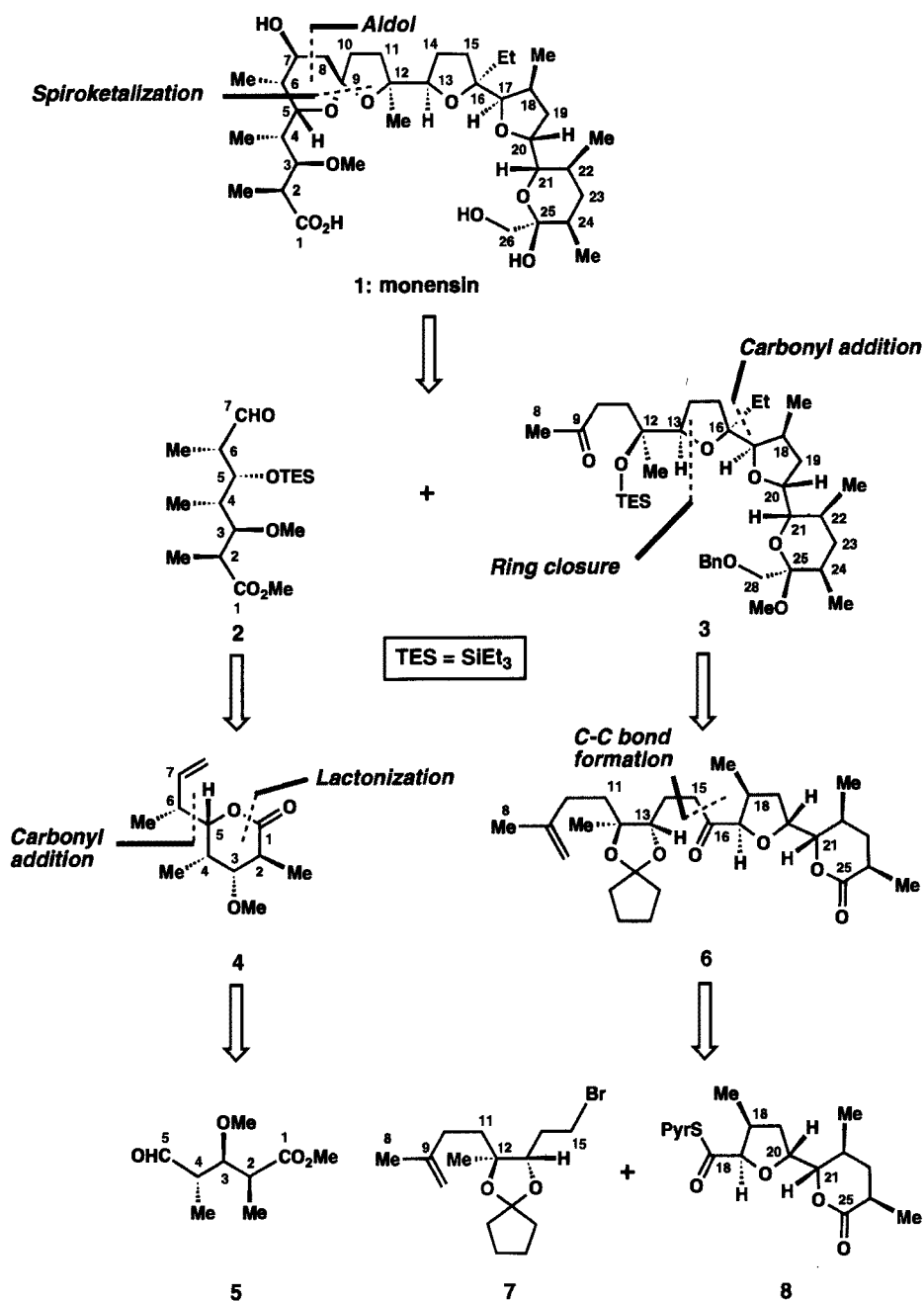
and is illustrated in Scheme 1 (see XI \rightarrow XIII). If we assume substituent X in generic ketone XI to be a heteroatom function (e. g. OH, OR, NR, NR₂, etc.), then the action of an organometallic reagent on XI should lead to the initial formation of a five-membered cyclic intermediate or chelate (see intermediate XII). Chelation of the type illustrated in XII not only enhances the electrophilic character of the carbonyl carbon, but it also prevents free rotation about the C(a)–C(b) bond and compels the organic nucleophile to add to the least hindered carbonyl diastereoface. Rigid chelate XII can be regarded as an ideal, albeit transient, cyclic template that permits efficient 1,2-asymmetric induction. Indeed, the degree of diastereoselectivity that attends α -chelation-controlled carbonyl addition reactions is often exceptional (for example, see XIV \rightarrow XV, Scheme 1).

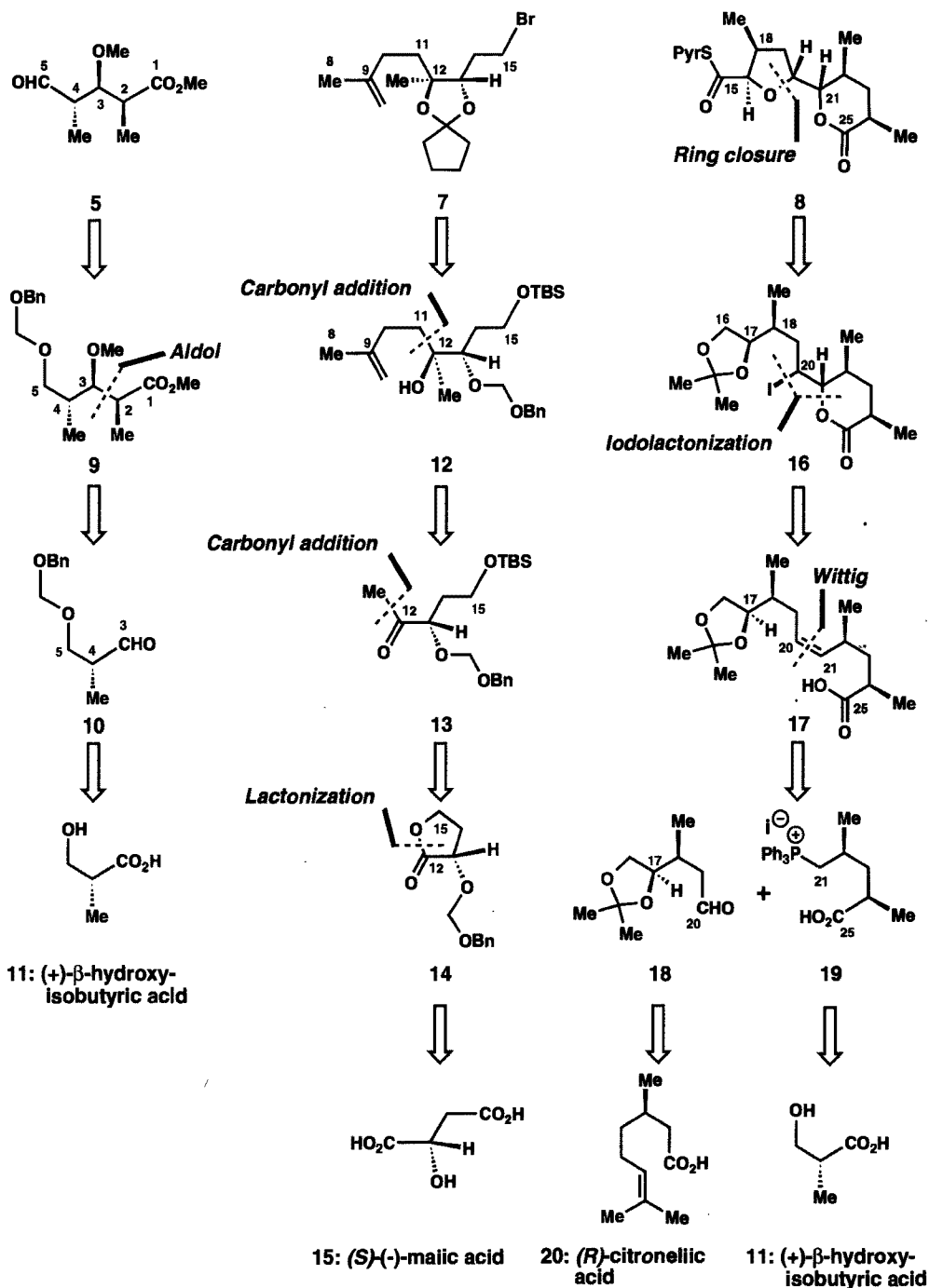
The highly stereoselective conversion of XIV to XV shown in Scheme 1 is but one of several examples that were disclosed in 1980 by W.C. Still and his group at Columbia.¹¹ These important studies defined experimental conditions under which consistently high values of α -asymmetric induction can be obtained in α -chelation-controlled carbonyl addition reactions. Chelation-controlled processes would appear to be particularly well suited for the creation of many of the vicinal stereochemical relationships found in the polyether antibiotics. The complex pattern of stereochemistry characteristic of this important class of natural products offers a formidable, yet irresistible, challenge to synthetic chemistry. Shortly after Kishi and coworkers disclosed the first total synthesis of the polyether antibiotic monensin,¹² W.C. Still *et al.* reported a second elegant synthesis of this naturally occurring substance.¹³ Below we discuss the general features of Still's convergent and enantiospecific monensin synthesis.

15.2 Retrosynthetic Analysis and Strategy

Monensin's highly oxygenated structure is distinguished by 17 stereocenters and a contiguous arrangement of a 1,6-dioxaspiro[4.5]-decane ring system, two tetrahydrofuran rings, and a functionalized tetrahydropyran ring. Retrosynthetic disassembly of monensin (**1**), in the manner illustrated in Scheme 2, provides intermediates **2** and **3** as potential precursors. Intermediate **2**, the left-wing fragment, contains carbons 1–7 of monensin and all of its stereochemical relationships are vicinal. On the other hand, intermediate **3**, the right-wing fragment, contains carbons 8–26 of the target molecule and it possesses vicinal as well as remote stereochemical relationships.

Although intermediate **2** is terminated at both ends by electrophilic carbonyl groups, the aldehydic function at C-7 is inherently more reactive, and thus more susceptible to a nucleophilic attack, than the methoxycarbonyl group at C-1. As a result, it should be possible to selectively engage the aldehyde carbonyl of intermedi-

**Scheme 2.** Retrosynthetic analysis of monensin (1).



Scheme 2. Retrosynthetic analysis of monensin (1) (continued).

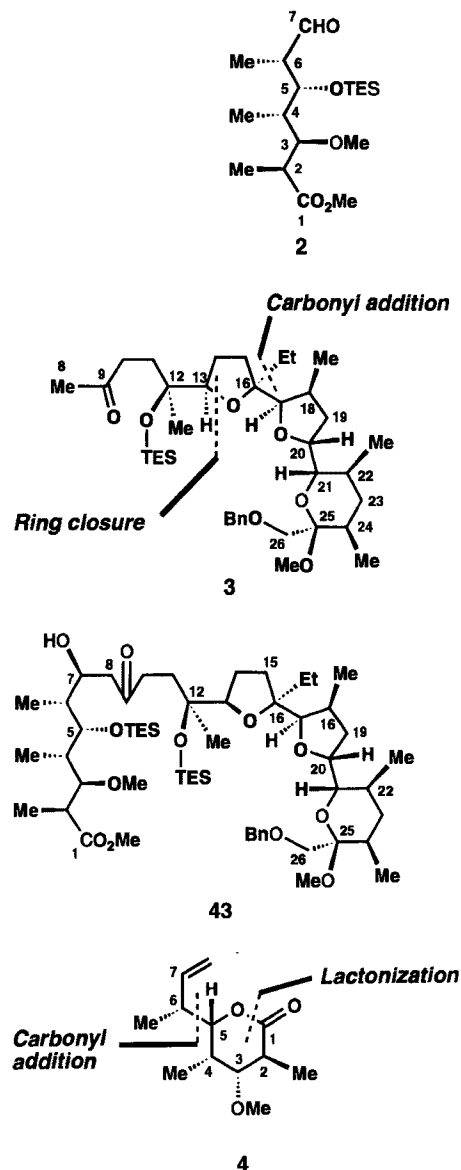
ate **2** in an aldol condensation with the kinetic enolate derived from methyl ketone **3**. The convergent union of intermediates **2** and **3**, in this manner, would accomplish the formation of a carbon-carbon bond between positions 7 and 8, and would afford a β -hydroxy ketone that contains all of the atoms found in monensin (see intermediate **43** in Scheme 7).

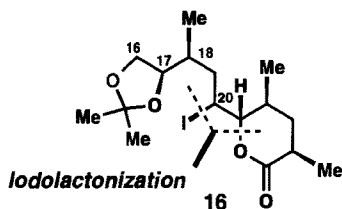
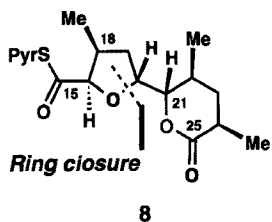
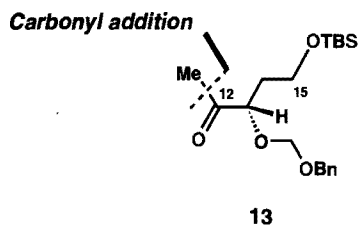
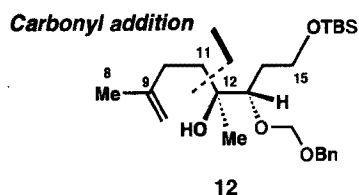
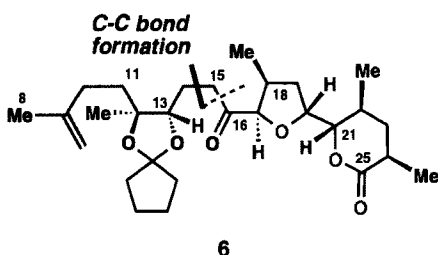
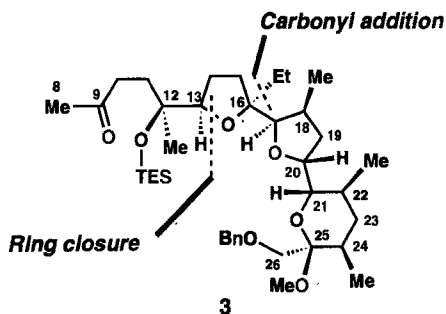
An important stereochemical issue presents itself here. *A priori*, an aldol condensation between intermediates **2** and **3** could result in the formation of a mixture of diastereomeric aldol adducts, epimeric at C-7, with little or no preference for a particular stereoisomer. Cram's rule^{2,4} predicts the formation of aldol adduct **43**. This intermediate possesses the correct absolute configuration at C-7, and it should be noted that Kishi *et al.* had demonstrated during the course of their monensin synthesis that a similar aldol condensation produced the desired C-7 epimer as the major product.¹²

From intermediate **43**, the path to monensin would seemingly be straightforward. A significant task which would remain would be the construction of the 1,6-dioxaspiro[4.5]decane substructure of monensin. You will note that the oxygen atoms affixed to carbons 5 and 12 in **43** reside in proximity to the ketone carbonyl at C-9. In such a favorable setting, it is conceivable that the action of acid on **43** could induce cleavage of both triethylsilyl ethers to give a keto triol which could then participate in a spontaneous, thermodynamically controlled spiroketalization reaction. Saponification of the C-1 methyl ester would then complete the synthesis of monensin.

Intermediate **2** could conceivably be derived from δ -lactone **4** (see Scheme 2). In the synthetic direction, saponification of the lactone ring in **4** followed by a short sequence of functional group manipulations could secure the formation of **2**. Retrosynthetic cleavage of the indicated bonds in **4** provides **5** as a plausible precursor. Like intermediate **2**, compound **5** is terminated at both ends by electrophilic carbonyl groups and both of these groupings could, in principle, react with a nucleophilic reagent. Nevertheless, the C-5 aldehyde carbonyl in **5** is the more competent electrophile and it would be expected to react more quickly with an external nucleophile than the C-1 methoxycarbonyl group. Subjection of intermediate **5** to a chemo- and stereoselective crotylation reaction could accomplish the introduction of carbons 6 and 7 of the target and the formation of the vicinal stereocenters at C-5 and at C-6. The initial products of the aldehyde addition step (i.e. intermediates **23** and **24** in Scheme 3), containing as they do a potentially nucleophilic aluminum alkoxide at C-5 and an electrophilic methoxycarbonyl group six atoms removed, are poised for a lactonization reaction to give the desired δ -lactone **4** and its diastereomer, lactone **25** (Scheme 3).

Through some conventional functional group manipulations, intermediate **5** could be derived from compound **9**. Retrosynthetic disassembly of intermediate **9**, in the manner illustrated in Scheme 2, furnishes the benzyloxymethyl ether of (*R*)- β -hydroxyisobutyraldehyde (**10**) as a potential precursor and introduces the interesting





possibility of creating the C2–C3 *syn* stereochemical relationship through an intermolecular aldol condensation with a propionate enolate or some equivalent. In turn, intermediate **10** can be traced to (+)- β -hydroxyisobutyric acid (**11**), and it was anticipated that a β -chelation-controlled addition process (see **21** + **10** \rightarrow **22** in Scheme 3) could guide the formation of the C-3 stereocenter in **9**. Since the geometry of the enolate derived from **21** would determine the configuration of the C-2 stereocenter in **9**, it is imperative that **21** be converted into a *Z* enolate.¹⁴

Still's synthesis of intermediate **3**, the right wing of monensin, was designed to be highly convergent (Scheme 2). Retrosynthetic cleavage of the indicated bonds in **3** provides keto lactone **6** as a viable precursor. The constitution of intermediate **6** is such that it ought to permit an α -chelation-controlled addition¹⁰ of ethylmagnesium bromide to the C-16 ketone carbonyl (see **6** \rightarrow **38** \rightarrow **39** in Scheme 6b). This stereocontrolled process would establish the stereogenic center at C-16 in **3**. An interesting sequence of functional group manipulations and an intramolecular etherification reaction with inversion of configuration at C-13 (see **40** \rightarrow **41** in Scheme 7) could then complete the synthesis of intermediate **3**. The disconnection illustrated in intermediate **6** (see Scheme 2) is particularly productive. In the synthetic direction, treatment of bromide **7** with magnesium metal, followed by acylation of the resultant Grignard reagent with thiopyridyl ester **8**, could furnish ketone **6**.

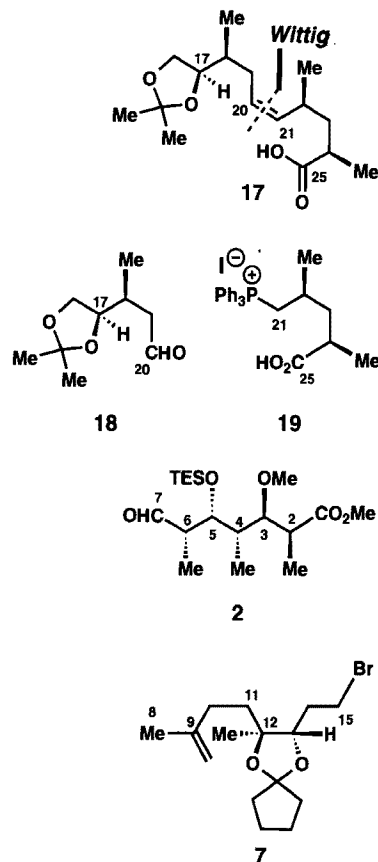
Retrosynthetic cleavage of the C11–C12 bond in intermediate **12**, the projected precursor of **7**, furnishes methyl ketone **13**. The Lewis-basic oxygen substituent at C-13 is a valuable structural feature of this intermediate. On the basis of Cram's pioneering work in the late 1950s⁹ and Still's important studies in the late 1970s¹¹ it was anticipated that α -alkoxy ketone **13** would be an excellent substrate for an α -chelation-controlled carbonyl addition reaction. In particular, it was projected that treatment of **13** with 3-methyl-3-butenylmagnesium bromide (see **13** \rightarrow **12** in Scheme 4) would result in the stereoselective formation of **12** through the intermediacy of a rigid, five-membered chelate. The chelated ketone illustrated in Scheme 4 is distinguished by a hindered *Re* diastereoface and a much more accessible *Si* diastereoface. There is good reason to believe that an organic nucleophile would add selectively to the less hindered *Si* face of the chelated ketone carbonyl (see arrow in Scheme 4) to give an adduct with the desired relative stereochemical relationship at carbons 12 and 13. Differentiated methyl ketone **13** could be fashioned in two steps from γ -lactone **14**, which is readily available in enantiomerically pure form from (*S*)-(-)-malic acid (**15**) (see Scheme 2).

Intermediate **8**, the projected electrophile in a coupling reaction with intermediate **7**, could conceivably be derived from iodolactone **16**. In the synthetic direction, cleavage of the acetonide protecting group in **16** with concomitant intramolecular etherification could result in the formation of the functionalized tetrahydrofuran ring of **8** (see **16** \rightarrow **37** in Scheme 6a). A Jones oxidation followed by con-

version of the resultant carboxyl group into a thiopyridyl ester would then complete the synthesis of intermediate **8**.

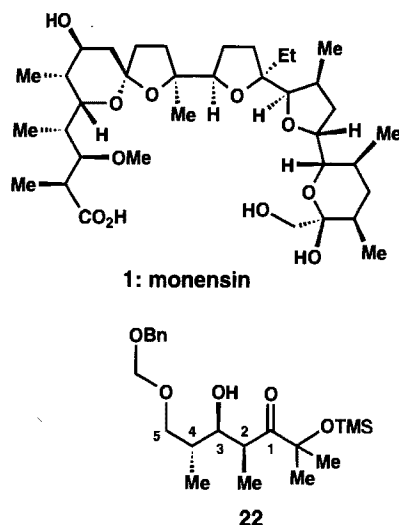
The adjacent iodine and lactone groupings in **16** constitute the structural prerequisite, or retron, for the iodolactonization transform.¹⁵ It was anticipated that the action of iodine on unsaturated carboxylic acid **17** would induce iodolactonization¹⁶ to give iodolactone **16**. The *cis* C20–C21 double bond in **17** provides a convenient opportunity for molecular simplification. In the synthetic direction, a Wittig reaction¹⁷ between the nonstabilized phosphorous ylide derived from **19** and aldehyde **18** could result in the formation of *cis* alkene **17**. Enantiomerically pure (*R*)-citronellic acid (**20**) and (+)- β -hydroxyisobutyric acid (**11**) are readily available sources of chirality that could be converted in a straightforward manner into optically active building blocks **18** and **19**, respectively.

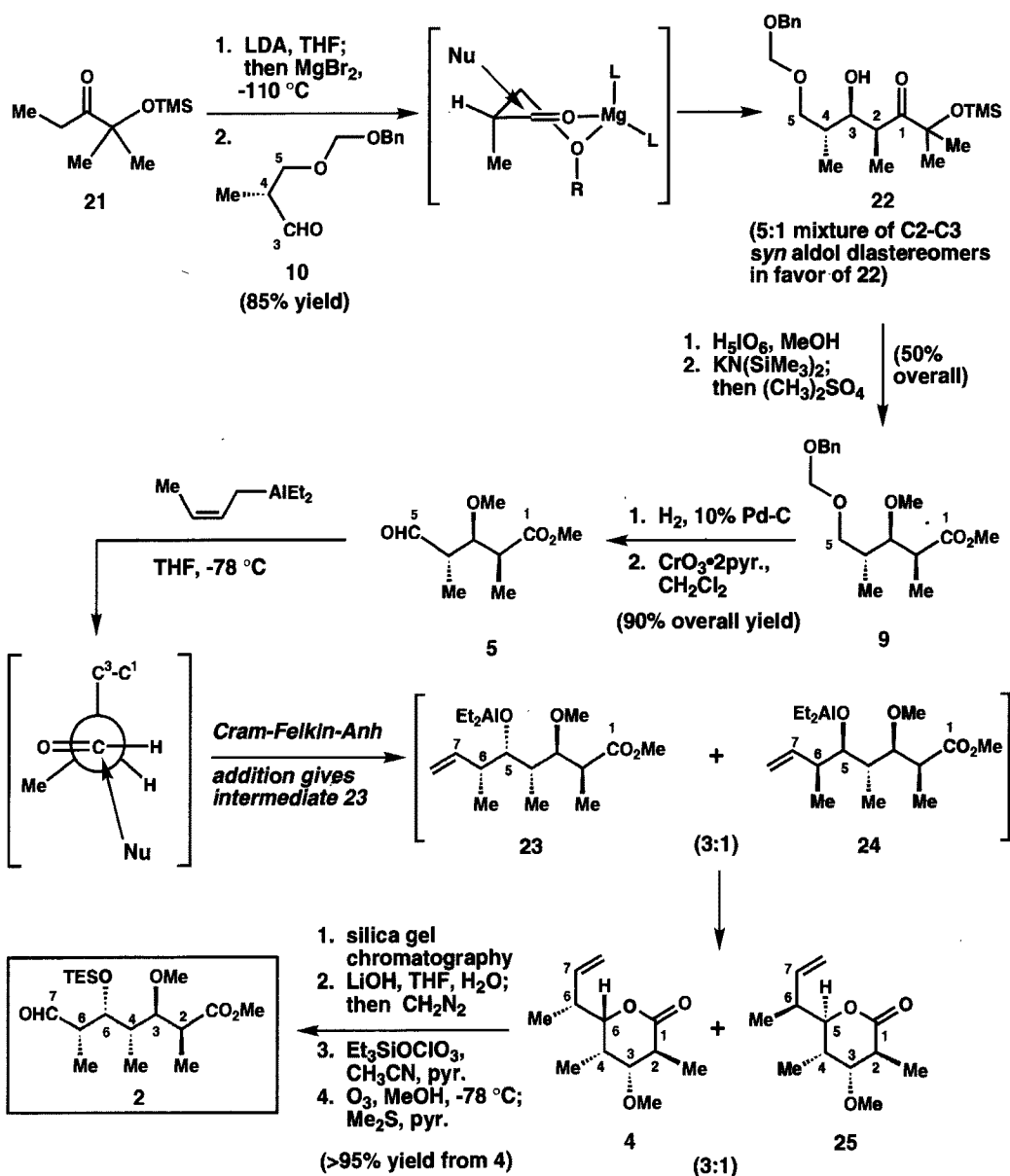
It is instructive to note that intermediates **2**, **7**, and **18** contain only vicinal stereogenic centers, and that all three can be traced to optically active precursors that are available in abundance from the chiral pool.¹⁸ Although the prospects for securing correct vicinal stereochemical relationships through the use of a preexisting stereocenter seem excellent, the task of establishing remote stereochemical relationships in monensin seems much less straightforward. Still's total synthesis of monensin provides a brilliant illustration of the principle of *stereochemical correlation*.¹⁹ Stereochemical correlation establishes remote stereochemical relationships through the union of optically active building blocks. Provided that each chiral building block is prepared in its correct absolute stereochemical form, then the relative stereochemical relationships created when these chiral intermediates are joined must necessarily be the required ones.



15.3 Total Synthesis

Still's synthesis of monensin (**1**) is based on the assembly and union of three advanced, optically active intermediates **2**, **7**, and **8**. It was anticipated that substrate-stereocontrolled processes could secure vicinal stereochemical relationships and that the coupling of the above intermediates would establish remote stereorelationships. Scheme 3 describes Still's synthesis of the left wing of monensin, intermediate **2**. This construction commences with an aldol reaction between the (*Z*) magnesium bromide enolate derived from 2-methyl-2-trimethylsilyloxy-3-pentanone (**21**) and benzyloxymethyl-protected (*R*)- β -hydroxyisobutyraldehyde (**10**).²⁰ The use of intermediate **21** in aldol reactions was first reported by Heathcock²¹ and, in this particular application, a 5:1 mixture of *syn* aldol diastereoisomers is formed in favor of the desired aldol adduct **22** (85% yield). The action of lithium diisopropylamide (LDA) and magnesium(II) bromide on **21** affords a (*Z*) magnesium enolate that





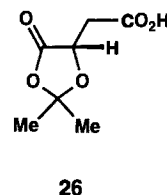
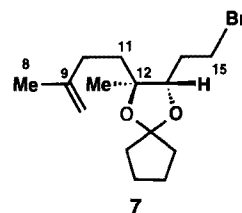
Scheme 3. Synthesis of intermediate 2.

preferentially adds to the less hindered diastereoface of the chelated aldehyde carbonyl of **10** (see Scheme 3). Exposure of the mixture of aldol diastereomers to periodic acid in methanol results in the formation of a mixture of β -hydroxy acids that is subsequently methylated to give intermediate **9** in a yield of 50% from **22**. It was convenient to purify intermediate **9** at this stage by medium pressure liquid chromatography on silica gel. Hydrogenolysis of the benzyloxymethyl protecting group in **9**, followed by oxidation of the resultant primary alcohol with Collins reagent, furnishes aldehyde **5** in 90% overall yield.

As we have alluded to earlier, molecules that possess more than one electrophilic site, such as intermediate **5**, could potentially react indiscriminately with a nucleophilic species. The electron-deficient aldehyde carbonyl at C-5 in intermediate **5** is, however, more reactive than the C-1 methoxycarbonyl group. In the presence of *cis*-2-butenyldiethylaluminum, a completely chemo- and modestly stereoselective crotylation reaction takes place, providing a 3:1 mixture of diastereomeric δ -lactones **4** and **25** after cyclization of the initial addition products **23** and **24**. It is important to note that the aluminum reagent employed in this reaction is incapable of bisligation (i.e. β -chelation not possible), and that the formation of the major diastereomer **23** is consistent with a Cram-Felkin-Anh model⁴ (see Scheme 3). After flash chromatographic purification,²² sequential treatment of a sample of **4** with ozone and Jones reagent provided a lactonic acid that was found to be identical with a monensin degradation product. In this manner, the structure and stereochemistry of δ -lactone **4** was confirmed.

The final stages in the synthesis of the left wing of monensin proceeded smoothly as follows. Saponification of the δ -lactone ring in **4** with lithium hydroxide, followed by esterification of the terminal carboxyl group with diazomethane, provides an open-chain hydroxy ester. Interestingly, during the course of monensin degradation studies,^{13a} it was found that the hindered free hydroxyl group at C-5 could not be protected by using trialkylsilyl chlorides under standard conditions. However, treatment of a solution of the open-chain hydroxy ester in acetonitrile with pyridine and triethylsilyl perchlorate²³ results in facile protection of the hindered secondary hydroxyl at C-5. Finally, oxidative cleavage of the terminal olefin with ozone provides key intermediate **2**, the left wing of monensin, in >95% yield from **4**.

Scheme 4 outlines the synthesis of key intermediate **7** in its correct absolute stereochemical form from readily available (*S*)-(-)-malic acid (**15**). Simultaneous protection of the contiguous carboxyl and secondary hydroxyl groups in the form of an acetonide proceeds smoothly with 2,2'-dimethoxypropane and *para*-toluenesulfonic acid and provides intermediate **26** as a crystalline solid in 75–85% yield. Chemoselective reduction of the terminal carboxyl group in **26** with borane–tetrahydrofuran complex ($\text{BH}_3 \cdot \text{THF}$) affords a primary hydroxyl group that attacks the proximal carbonyl group, upon acidification, to give a hydroxybutyrolactone. Treat-





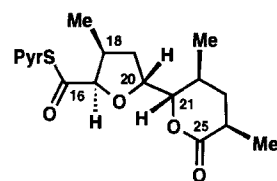
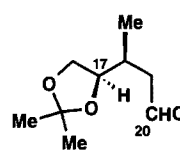
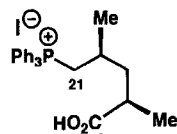
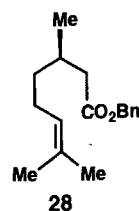
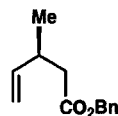
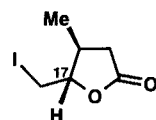
ment of this substance with benzyloxymethyl chloride and Hünig's base provides intermediate **14** in 75 % yield from **26**.

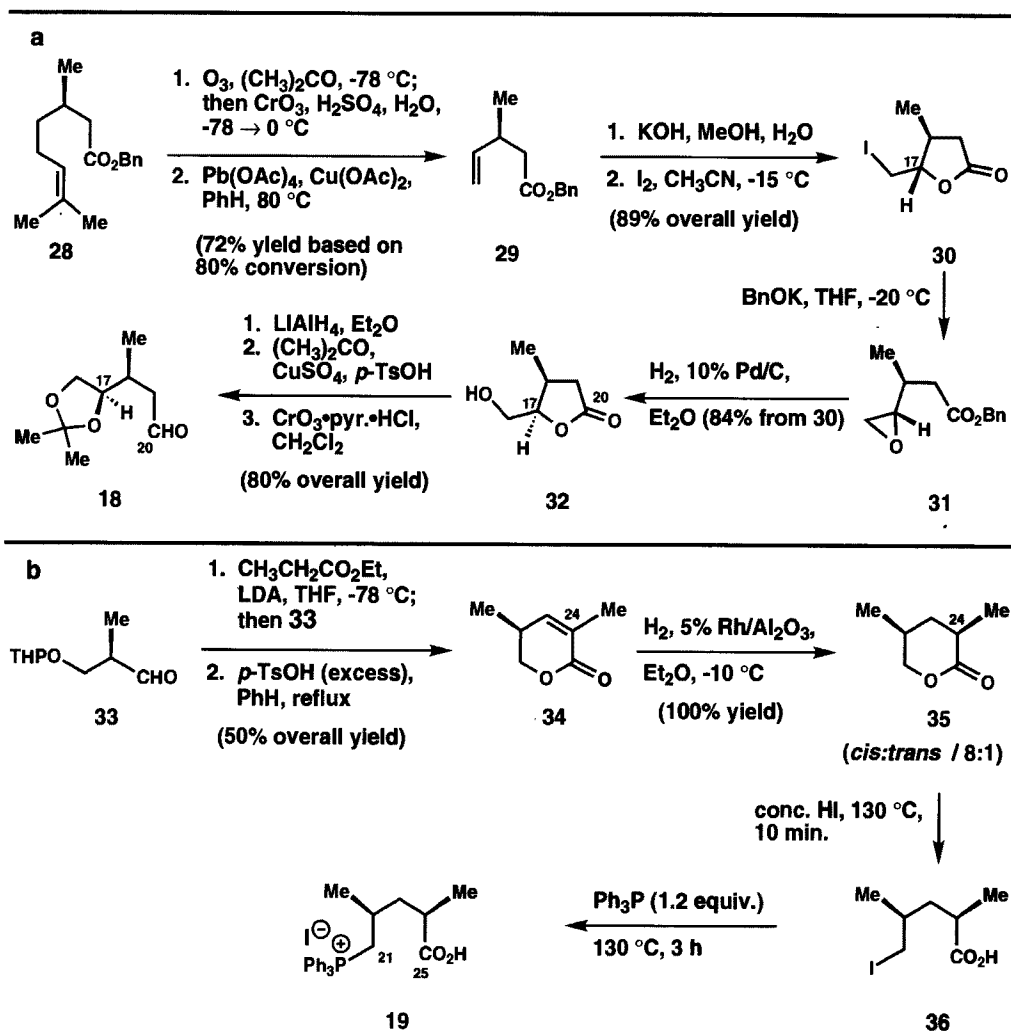
When γ -lactone **14** is treated with methylmagnesium bromide in THF at -78°C , a carbonyl addition reaction takes place and gives, after aqueous workup, a hemiketal that is subsequently converted to **13** on treatment with *tert*-butyldimethylsilyl chloride. It is noteworthy that a tertiary alcohol by-product resulting from the attack of a second equivalent of Grignard reagent is not produced. Evidently, the tetrahedral intermediate that forms on addition of one equivalent of methylmagnesium bromide to the lactone carbonyl in **14** is sufficiently stable at -78°C , thereby preventing the addition of a second equivalent of the reagent.

Ketone **13** possesses the requisite structural features for an α -chelation-controlled carbonyl addition reaction.⁹⁻¹¹ Treatment of **13** with 3-methyl-3-butenylmagnesium bromide leads, through the intermediacy of a five-membered chelate, to the formation of intermediate **12** together with a small amount of the C-12 epimer. The degree of stereoselectivity (*ca.* 50:1 in favor of the desired compound **12**) exhibited in this substrate-stereocontrolled addition reaction is exceptional. It is instructive to note that sequential treatment of lactone **14** with 3-methyl-3-butenylmagnesium bromide and *tert*-butyldimethylsilyl chloride, followed by exposure of the resultant ketone to methylmagnesium bromide, produces the C-12 epimer of intermediate **12** with the same 50:1 stereoselectivity.

From intermediate **12**, the path to key intermediate **7** is straightforward. Reductive removal of the benzyloxymethyl protecting group in **12** with lithium metal in liquid ammonia provides diol **27** in an overall yield of 70 % from **14**. Simultaneous protection of the vicinal hydroxyl groups in **27** in the form of a cyclopentanone ketal is accompanied by cleavage of the *tert*-butyldimethylsilyl ether. Treatment of the resultant primary alcohol with *N*-bromosuccinimide (NBS) and triphenylphosphine accomplishes the formation of bromide **7**, the central fragment of monensin, in 71 % yield from **27**.

A cursory inspection of key intermediate **8** (see Scheme 1) reveals that it possesses both vicinal and remote stereochemical relationships. To cope with the stereochemical challenge posed by this intermediate and to enhance overall efficiency, a convergent approach featuring the union of optically active intermediates **18** and **19** was adopted. Scheme 5a illustrates the synthesis of intermediate **18**. Thus, oxidative cleavage of the trisubstituted olefin of (*R*)-citronellic acid benzyl ester (**28**) with ozone, followed by oxidative workup with Jones reagent, affords a carboxylic acid which can be oxidatively decarboxylated to **29** with lead tetraacetate and copper(II) acetate. Saponification of the benzyl ester in **29** with potassium hydroxide provides an unsaturated carboxylic acid which undergoes smooth conversion to *trans* iodolactone **30** on treatment with iodine in acetonitrile at -15°C (89 % yield from **29**).²⁴ The diastereoselectivity of the thermodynamically controlled iodolactonization reaction is approximately 20:1 in favor of the more stable *trans* iodolactone **30**.

**8****18****19****28****29****30**



Scheme 5. Synthesis of intermediates **18** (a) and **19** (b).

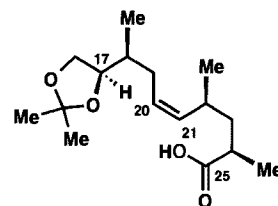
You will note that the configuration of the newly created oxygen-bearing stereocenter at C-17 (monensin numbering) in **30** is opposite to the corresponding stereocenter in intermediate **18**. Therefore, at some stage during the course of the conversion of **30** to **18**, an inversion of stereochemistry at position 17 must be achieved. Treatment of iodolactone **30** with the potassium salt of benzyl alcohol results in the formation of epoxy benzyl ester **31**. Interestingly, hydrogenolysis of the benzyl ester moiety in **31** is accompanied by spontaneous lactonization to give hydroxy lactone **32** with the correct configuration at C-17 and in 84 % yield from **30**. Treatment of **32** with lithium aluminum hydride accomplishes a complete reduction of the lactone function and provides a triol. The presence of three hydroxyl groups in a synthetic intermediate could conceivably create serious differentiation problems. In this context, however, two of the three hydroxyl groups are affixed to adjacent carbons and can thus be simultaneously protected in the form of an acetonide ring by using acetone and an acid catalyst. Finally, oxidation of the C-20 primary hydroxyl group with pyridinium dichromate in CH_2Cl_2 provides key intermediate **18** (80 % from **32**).

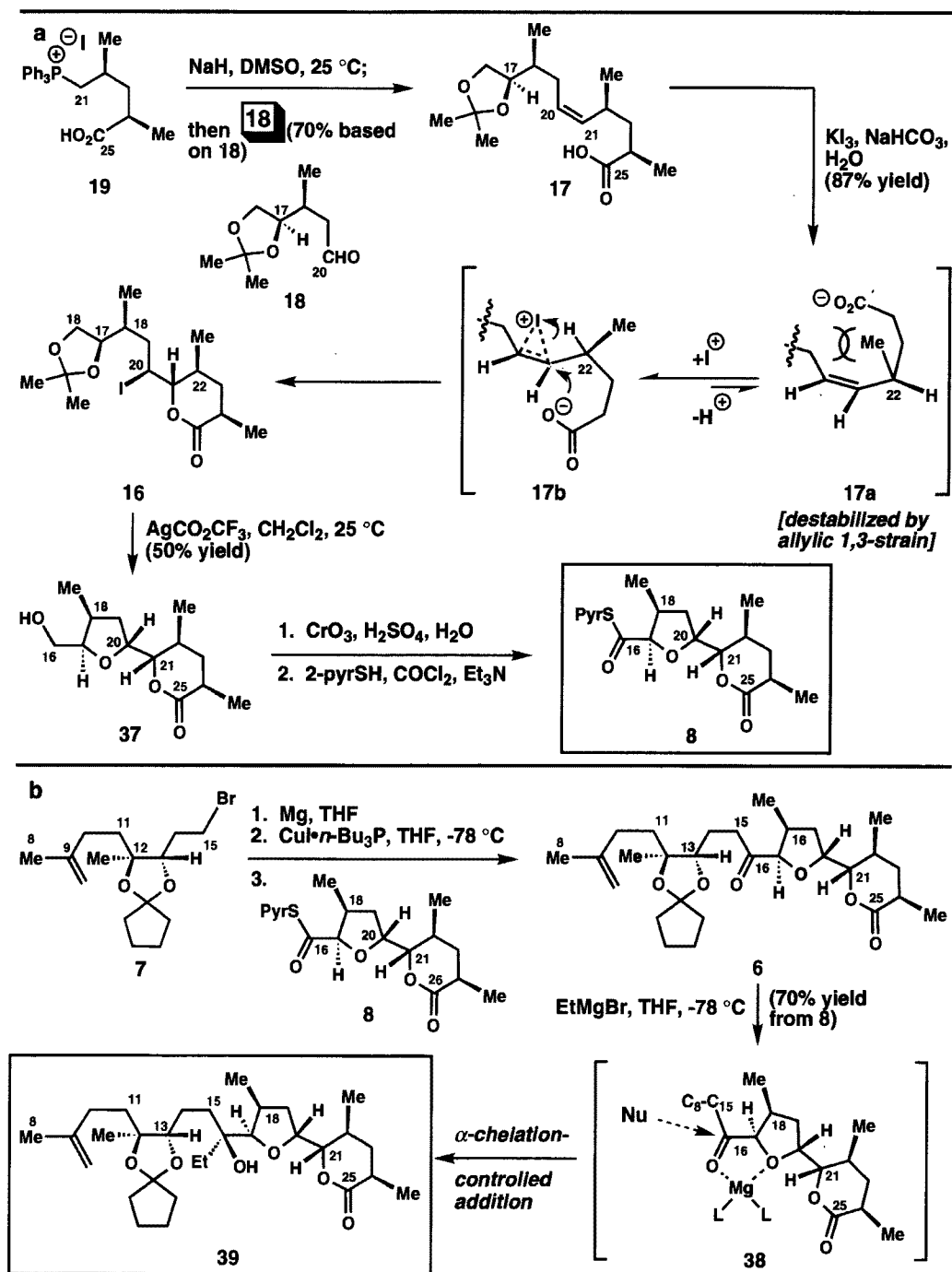
The synthesis of intermediate **19** commences with aldehyde **33** (see Scheme 5b), a substance readily available in enantiomerically pure form from (+)- β -hydroxyisobutyric acid (**11**)²⁰. Exposure of **33** to the lithium enolate of ethyl propionate, followed by treatment of the resultant aldol condensation product with excess *para*-toluenesulfonic acid in refluxing benzene, results in the formation of unsaturated lactone **34** in 50 % overall yield. Although a ratio of aldol stereoisomers was not reported, the stereogenic center created in the aldol condensation is destroyed during the course of the next step through dehydration.

Unsaturated δ -lactone **34** adopts a well-defined conformation and provides a suitable platform for the introduction of the stereogenic center at C-24' (monensin numbering). Catalytic hydrogenation of the carbon-carbon double bond in **34** takes place preferentially from the less hindered side of the molecule and provides an 8:1 mixture of stereoisomers in favor of **35** (100 % yield). Cleavage of δ -lactone **35** with concentrated hydriodic acid at 130 °C, followed by treatment of the resultant iodide **36** with triphenylphosphine, completes the synthesis of intermediate **19**.

Intermediates **18** and **19** are comparable in complexity and complementary in reactivity. Treatment of a solution of phosphonium iodide **19** in DMSO at 25 °C with several equivalents of sodium hydride produces a deep red phosphorous ylide which couples smoothly with aldehyde **18** to give *cis* alkene **17** accompanied by ~20 % of the undesired *trans* olefin (see Scheme 6a). This reaction is an example of the familiar Wittig reaction,¹⁷ a most powerful carbon-carbon bond forming process in organic synthesis.

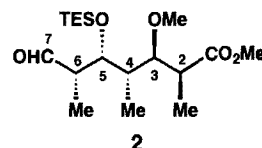
Unsaturated carboxylic acid **17** possesses the requisite structural features for an iodolactonization reaction.¹⁶ A source of electrophilic iodine could conceivably engage either diastereoface of the $\Delta^{20,21}$ double bond in **17**. The diastereomeric iodonium ion inter-





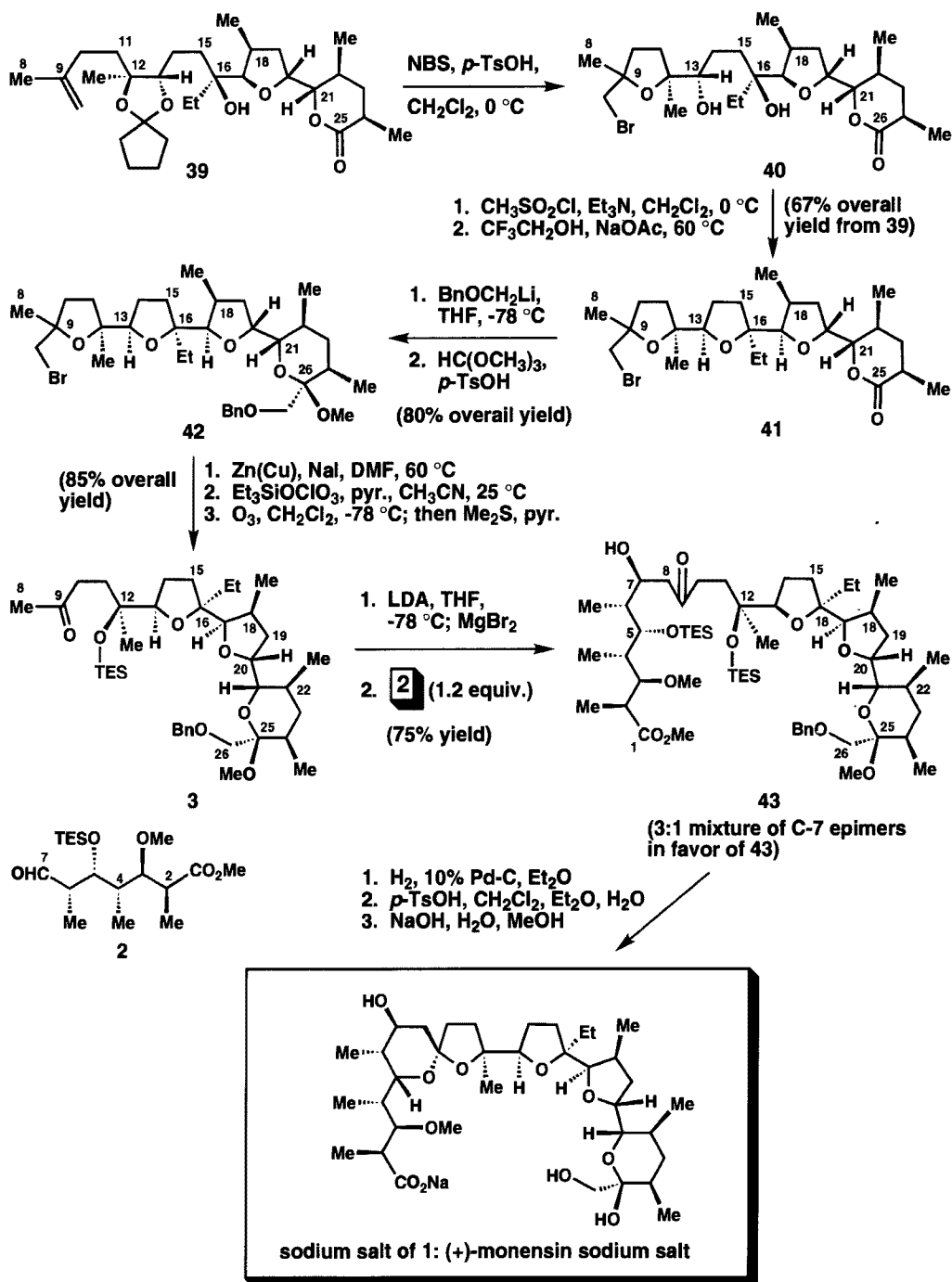
Scheme 6. Synthesis of intermediates 8 (a) and 39 (b).

mediates thus formed would then elicit an intramolecular, backside attack by the proximal carboxylate ion to give a mixture of diastereomeric iodolactones. However, of the two relevant conformations for intermediate **17**, conformer **17a** is significantly destabilized by allylic 1,3-strain.²⁵ The conformational equilibrium should therefore lie substantially in favor of **17b**, resulting in a highly diastereoselective iodolactonization reaction (see arrows in Scheme 6a). In the event, treatment of **17** with aqueous potassium triiodide and sodium bicarbonate induces iodolactonization and furnishes a single iodolactone stereoisomer, intermediate **16**, in 87% yield. Activation of the carbon–iodine bond in **16** with silver(I) ion is accompanied by rupture of the acetonide ring and spontaneous intramolecular attack at C-20, with inversion of configuration, to give tetrahydrofuran lactone **37** in 50% yield. Intermediate **37** was found to be identical with authentic material obtained by degradation of monensin. Finally, Jones oxidation of **37**, followed by conversion of the resultant carboxyl function to the corresponding thiopyridyl ester through the application of Corey's procedure,²⁶ provides key intermediate **8**.



We have retraced the elegant sequences of reactions leading to enantiospecific syntheses of intermediates **2**, **7**, and **8**. We are now in a position to address the union of these intermediates and the completion of the total synthesis of monensin (**1**). Bromide **7** is a versatile synthetic intermediate that can either be used as an alkylating agent or, alternatively, as a precursor for a nucleophilic organometallic reagent. Reduction of the carbon–bromine bond in **7** with magnesium metal furnishes a Grignard reagent, a competent carbon nucleophile, which couples smoothly with thiopyridyl ester **8** in the presence of cuprous iodide tri-*n*-butylphosphine complex to give ketone **6** (see Scheme 6b). One might approach a coupling reaction of this type with some trepidation because intermediate **8** possesses two electrophilic carbonyl groups, and both could react with a strong nucleophile. The thiopyridyl ester moiety in **8** is, however, more susceptible to nucleophilic attack than the lactone carbonyl. The inherent acylating potential of a thioester closely approximates that of a carboxylic acid anhydride.²⁷ Developed by Mukaiyama *et al.* in the early 1970s,²⁸ the reaction of a Grignard reagent with a thiopyridyl ester to give a ketone is an effective process in organic synthesis.

The Lewis-basic ether oxygen attached to C-17 in **6** is a valuable structural feature. In the presence of an organometallic reagent, the ether oxygen at C-17 and the adjacent ketone carbonyl oxygen can simultaneously associate with the metal counterion to give a rigid, five-membered chelate (see intermediate **38**, Scheme 6b). Chelation of the type illustrated in **38** serves two important functions. First, it enhances the electrophilic character of the ketone carbonyl carbon and facilitates an attack by a nucleophile. Second, it prevents free rotation about the C16–C17 bond and creates a strong diastereofacial bias. Treatment of a solution of intermediate **6** in THF at -78°C with ethylmagnesium bromide results in the formation of



Scheme 7. Synthesis of (+)-monensin sodium salt (sodium salt of 1).

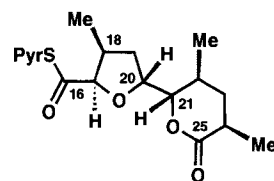
tertiary alcohol **39** through the intermediacy of chelate **38** (70% yield from **8**). In this α -chelation-controlled carbonyl addition reaction, complete 1,2-asymmetric induction is observed; intermediate **39** is the only stereoisomer formed.

Interestingly, treatment of a solution of **39** in CH_2Cl_2 with *para*-toluenesulfonic acid and *N*-bromosuccinimide induces cleavage of the ketal protecting group with concomitant bromoetherification and provides intermediate **40** (see Scheme 7). In this manner, the tertiary hydroxyl groups at C-12 and at C-16 can be easily differentiated. Selective mesylation of the less hindered secondary hydroxyl group in **40**, followed by intramolecular etherification, with inversion of configuration at C-13, furnishes intermediate **41** in 67% yield from **39**. The spectroscopic properties and chromatographic behavior of intermediate **41** were found to be identical with those of authentic material derived from the natural product.

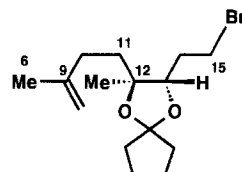
The C-25 lactone carbonyl group is worthy of special comment. The electron-deficient nature of a carbonyl carbon atom predisposes a lactone to a nucleophilic attack and confers lability to adjacent carbon-hydrogen bonds. Lactones that contain a stereogenic center in the α position are thus susceptible to racemization/epimerization, provided, of course, that reprotonation of the lactone enolate occurs with no facial selectivity. Despite the properties of the carbonyl group which make the lactone function susceptible to destructive reaction processes, the C-25 lactone carbonyl in intermediate **8** does not induce any undesirable reaction during the course of the convergent coupling of intermediates **7** and **8** (see Scheme 6b); neither nucleophilic attack at C-25 nor epimerization at C-24 occurs during this crucial coupling reaction. Likewise, the action of ethylmagnesium bromide on intermediate **6** smoothly accomplishes the formation of tertiary alcohol **39** without disturbing either the lactone function or the C-24 stereocenter.

As inert as the C-25 lactone carbonyl has been during the course of this synthesis, it can serve the role of electrophile in a reaction with a nucleophile. For example, addition of benzyloxymethyl-lithium²⁹ to a cold (-78°C) solution of **41** in THF, followed by treatment of the intermediate hemiketal with methyl orthoformate under acidic conditions, provides intermediate **42** in 80% overall yield. Reduction of the carbon-bromine bond in **42** with concomitant β -elimination of the C-9 ether oxygen is achieved with Zn-Cu couple and sodium iodide at 60°C in DMF. Under these reaction conditions, it is conceivable that the bromine substituent in **42** is replaced by iodine, after which event reductive elimination occurs. Silylation of the newly formed tertiary hydroxyl group at C-12 with triethylsilyl perchlorate, followed by oxidative cleavage of the olefin with ozone, results in the formation of key intermediate **3** in 85% yield from **42**.

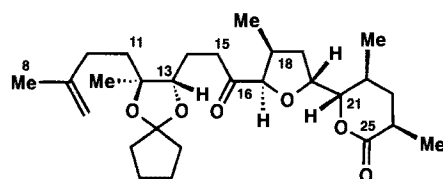
We have reached a critical stage in the synthesis. Intermediates **2** and **3** represent the left- and right-wing sectors of monensin, respectively. Taken together, these two key building blocks account for 15 of monensin's 17 stereogenic centers, and both are suitably



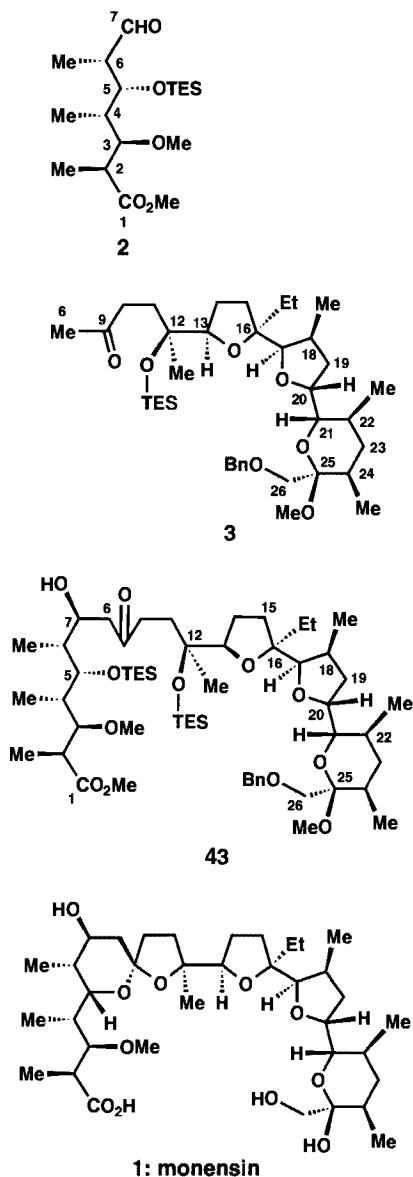
8



7



6



differentiated and are amenable to further advance. It was anticipated at the outset that intermediates **2** and **3** could be joined by means of an aldol condensation. This operation would simultaneously create the C7–C8 bond and the hydroxyl-bearing stereocenter at C-7. As inviting as this possibility was, the stereochemical course of the crucial aldol condensation could not be predicted with certainty. Nevertheless, it seemed reasonable to suppose that the branched nature of C-5 and the steric bulk of the C-5 triethylsilyl ether would prevent a chelation-controlled process. The preferred and desired stereochemical course of the aldol reaction would then be consistent with a Cram-Felkin-Anh model. Moreover, it is important to note that Kishi *et al.* demonstrated in their synthesis of monensin¹² that a similar aldol condensation gave, as the major product, a β -hydroxy ketone that possessed the requisite (*R*) configuration at C-7. In the event, when the kinetic magnesium enolate derived from **3** is exposed to 1.2 equivalents of **2**, the crucial intermolecular aldol condensation occurs and provides a 3:1 mixture of diastereomeric aldol adducts in favor of **43** (75% yield) (Scheme 7).

You will note that the oxygen atoms attached to carbons 5 and 12 in **43** reside in proximity to the C-9 ketone carbonyl. Under sufficiently acidic conditions, it is conceivable that removal of the triethylsilyl protecting groups would be attended by a thermodynamically controlled spiroketalization reaction.³⁰ Indeed, after hydrogenolysis of the C-26 benzyl ether in **43**, subjection of the organic residue to the action of *para*-toluenesulfonic acid in a mixture of methylene chloride, ether, and water accomplishes the desired processes outlined above and provides monensin methyl ester. Finally, saponification of the methyl ester with aqueous sodium hydroxide in methanol furnishes the sodium salt of (+)-monensin [(+)-**1**]. Still's elegant synthesis of monensin is now complete.¹³

15.4 Conclusion

The instructive total synthesis of monensin by Still and coworkers employs a wealth of chemo- and stereoselective operations, and utilizes two powerful, yet distinct, strategies for solving stereochemical problems. The daunting task of establishing remote stereochemical relationships in monensin is mastered by coupling prefabricated optically active building blocks (i.e. *stereochemical correlation*¹⁹). By contrast, the vicinal stereochemical relationships in monensin are secured through purely substrate-stereocontrolled processes (i.e. *stereochemical communication*¹⁸). Interestingly, of the 17 stereocenters found in monensin, only the methyl-bearing stereocenters at carbons 4, 18, and 22 are derived from the chiral pool. The other 14 stereocenters are fashioned through substrate-stereocontrolled reactions.

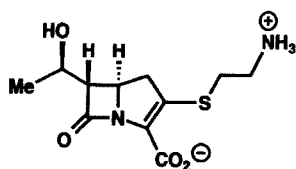
In one instance (see **2+3→43** in Scheme 7), the convergent coupling event is attended by the formation of a new stereocenter at C-7. Although the formation of this new stereocenter is guided by preexisting asymmetry in one of the coupling partners, the management of remote stereorelationships is accomplished through stereochemical correlation. The judicious choice of optically active starting materials and the extensive use of chelation-controlled reactions are both noteworthy features of this impressive synthesis.

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16



1: thienamycin

Merck (1980)

Thienamycin

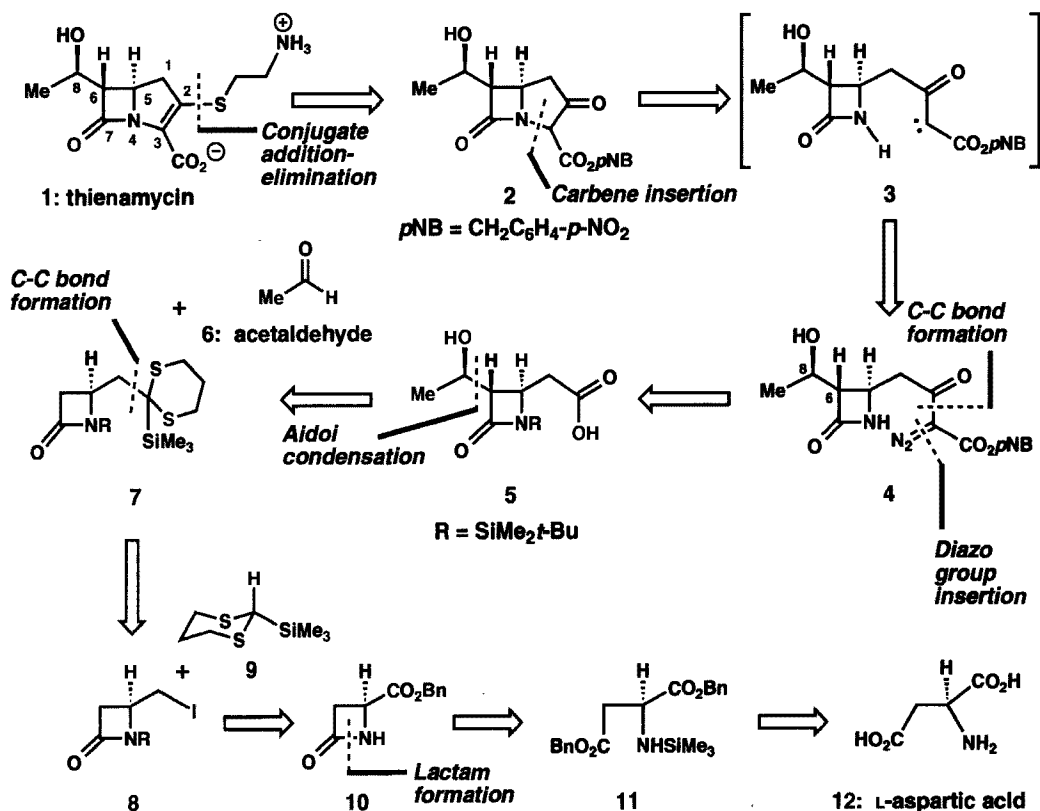
16.1 Introduction

In the late 1970s, scientists at Merck disclosed the potent antibacterial properties¹ and the structure² of the β -lactam antibiotic thienamycin (**1**). This compound is a constituent of fermentation broths of the soil microorganism, *Streptomyces cattleya*, and it displays activity against *Pseudomonas* and β -lactamase-producing species. Thienamycin is a zwitterionic compound, and its novel carbapenem structure, including absolute stereochemistry, was deduced on the basis of chemical, spectroscopic, and X-ray crystallographic studies.

In this chapter, we address the Merck synthesis of (+)-thienamycin (**1**).³ The development of this elegant synthesis was guided by the following realizations: (a) it is necessary to defer construction of thienamycin's carbapenem framework to a late stage in the synthesis by virtue of its rather unstable and reactive nature; (b) it would be advantageous to append the cysteamine and hydroxyethyl side chains at carbons 2 and 6, respectively, to a preformed ring system so that analogs could be readily prepared; and (c) it is desirable to develop an enantiospecific synthesis of thienamycin from a readily available, enantiomerically pure starting material. With these objectives in mind, the Merck group developed a highly efficient, novel, and enantiospecific synthesis of thienamycin. We begin with a discussion of the general strategy outlined retrosynthetically below.

16.2 Retrosynthetic Analysis and Strategy

The strained bicyclic carbapenem framework of thienamycin is the host of three contiguous stereocenters and several heteroatoms (Scheme 1). Removal of the cysteamine side chain affixed to C-2 furnishes β -keto ester **2** as a possible precursor. The intermolecular attack upon the keto function in **2** by a suitable thiol nucleophile could result in the formation of the natural product after dehydration of the initial tetrahedral adduct. In a most interesting and productive retrosynthetic maneuver, intermediate **2** could be traced in one step to α -diazo keto ester **4**. It is important to recognize that diazo compounds, such as **4**, are viable precursors to electron-deficient carbenes. In the synthetic direction, transition metal catalyzed decomposition of diazo keto ester **4** could conceivably furnish electron-deficient carbene **3**; the intermediacy of **3** is expected to be brief, for it should readily insert into the proximal N-H bond to



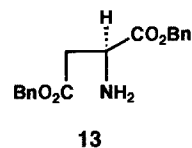
Scheme 1. Retrosynthetic analysis of thienamycin (1).

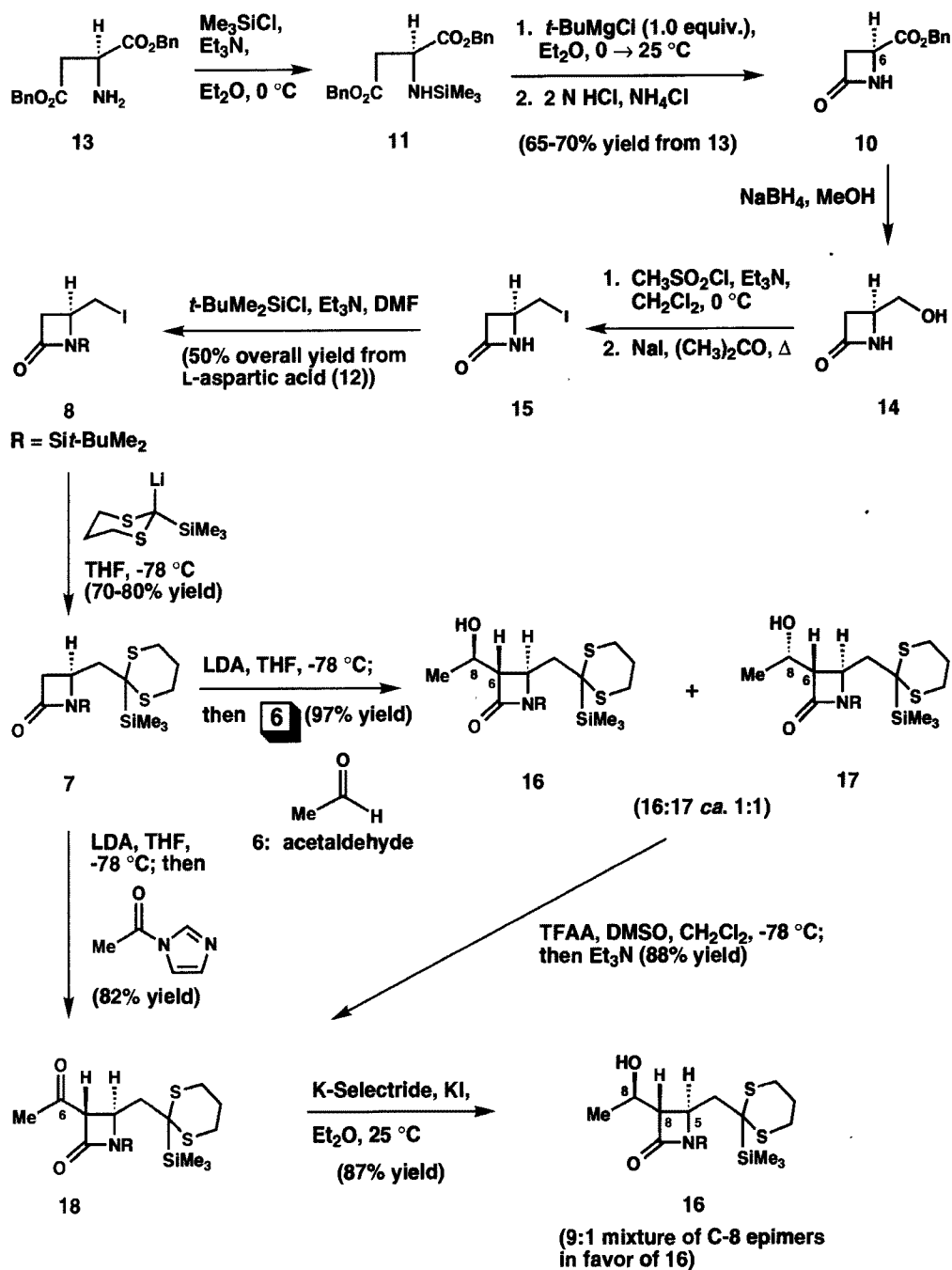
give **2**. This approach to the bicyclic nucleus of thienamycin is novel, and is strategically very different from Merck's first-generation synthesis of thienamycin which relied on the creation of a bond between C-2 and C-3 to achieve bicycle formation.⁴ It is instructive to draw attention to the β -hydroxy carbonyl moiety in intermediate **5**, the projected precursor of diazo keto ester **4**. This functional group relationship constitutes the retron for the aldol condensation transform.⁵ Thus, cleavage of the indicated bond in **5** furnishes monosubstituted β -lactam **7** and acetaldehyde (**6**) as potential precursors. In the synthetic direction, deprotonation of **7** at the site adjacent to the electron-withdrawing lactam carbonyl with a suitable base would furnish a lactam enolate which could be employed in an intermolecular aldol condensation with acetaldehyde (**6**). This event would result in the formation of the C6–C8 bond and would accomplish the introduction of the remaining two contiguous stereocenters.

The trimethylsilyl dithiane moiety is a conspicuous feature of intermediate **7**. In addition to its role as a stable surrogate for a carboxyl function, this group provides a convenient opportunity for molecular simplification. Retrosynthetic cleavage of the indicated carbon–carbon bond in **7** furnishes intermediates **8** and **9** as potential precursors. The anion-stabilizing properties of the dithiane group in **9** should permit the formation of the corresponding carbanion, the conjugate base of **9**. The carbanion formed by deprotonation of **9** could then be used as a nucleophile in a coupling reaction with alkyl iodide **8**, a suitable electrophile. The convergent union of intermediates **8** and **9**, in this manner, would result in the formation of the C1–C2 bond of thienamycin. Through some straightforward functional group manipulations, iodide **8** could be formed from lactam ester **10**. Amino diester **11** is derived retrosynthetically from **10** and could conceivably be elaborated in short order from inexpensive and readily available L-aspartic acid (**12**).

16.3 Total Synthesis

Merck's thienamycin synthesis commences with mono *N*-silylation of dibenzyl aspartate (**13**, Scheme 2), the bis(benzyl) ester of aspartic acid (**12**). Thus, treatment of a cooled (0 °C) solution of **13** in ether with trimethylsilyl chloride and triethylamine, followed by filtration to remove the triethylamine hydrochloride by-product, provides **11**. When **11** is exposed to the action of one equivalent of *tert*-butylmagnesium chloride, the active hydrogen attached to nitrogen is removed, and the resultant anion spontaneously condenses with the electrophilic ester carbonyl four atoms away. After hydrolysis of the reaction mixture with 2 *N* HCl saturated with ammonium chloride, enantiomerically pure azetidinone ester **10** is formed in 65–70% yield from **13**. Although it is conceivable that





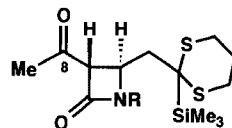
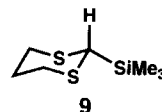
Scheme 2. Synthesis of intermediate 16.

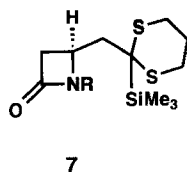
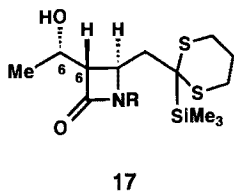
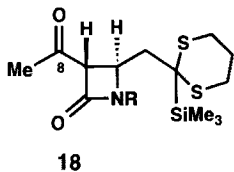
racemization at C-5 could have occurred during the course of the conversion of **11** to **10**, it was found by chemical correlation that no such event takes place during this transformation.

Intermediate **10** must now be molded into a form suitable for coupling with the anion derived from dithiane **9**. To this end, a chemoselective reduction of the benzyl ester grouping in **10** with excess sodium borohydride in methanol takes place smoothly and provides primary alcohol **14**. Treatment of **14** with methanesulfonyl chloride and triethylamine affords a primary mesylate which is subsequently converted into iodide **15** with sodium iodide in acetone. Exposure of **15** to *tert*-butyldimethylsilyl chloride and triethylamine accomplishes protection of the β -lactam nitrogen and leads to the formation of **8**. Starting from L-aspartic acid (**12**), the overall yield of **8** is approximately 50%, and it is noteworthy that this reaction sequence can be performed on a molar scale.

The dithiane moiety is a familiar protecting group for the carbonyl function.⁶ When it is used to mask the carbonyl group of an aldehyde, the dithiane function can actually alter the reactivity potential of the molecule. The sulfur atoms of a dithiane confer lability to the hydrogen atom that was formerly aldehydic; in the presence of a strong base (e.g. *n*-butyllithium), this hydrogen can be removed as a proton leaving behind a carbanion which is stabilized by the polarizable sulfur atoms.⁷ Dithiane-stabilized carbanions are valuable carbon nucleophiles in organic synthesis, and are synthetically equivalent to acyl anions because the carbonyl group can be easily regenerated from the dithiane after the key bond-forming event. The use of an aldehyde-derived dithiane as a precursor for a carbanion permits a *reactivity umpolung*;⁸ the formerly electrophilic aldehyde carbonyl carbon is converted into a competent nucleophile through the intermediacy of a dithiane. It is as if the inherent polarization of the aldehyde carbonyl has been reversed.

When 2-lithio-2-(trimethylsilyl)-1,3-dithiane,⁹ formed by deprotonation of **9** with an alkylolithium base, is combined with iodide **8**, the desired carbon-carbon bond forming reaction takes place smoothly and gives intermediate **7** in 70–80% yield (Scheme 2). Treatment of **7** with lithium diisopropylamide (LDA) results in the formation of a lactam enolate which is subsequently employed in an intermolecular aldol condensation with acetaldehyde (**6**). The union of intermediates **6** and **7** in this manner provides a 1:1 mixture of diastereomeric *trans* aldol adducts **16** and **17**, epimeric at C-8, in 97% total yield. Although stereochemical assignments could be made for both aldol isomers, the development of an alternative, more stereoselective route for the synthesis of the desired aldol adduct (**16**) was pursued. Thus, enolization of β -lactam **7** with LDA, as before, followed by acylation of the lactam enolate carbon atom with *N*-acetylimidazole, provides intermediate **18** in 82% yield. Alternatively, intermediate **18** could be prepared in 88% yield, through oxidation of the 1:1 mixture of diastereomeric aldol adducts **16** and **17** with trifluoroacetic anhydride (TFAA) in

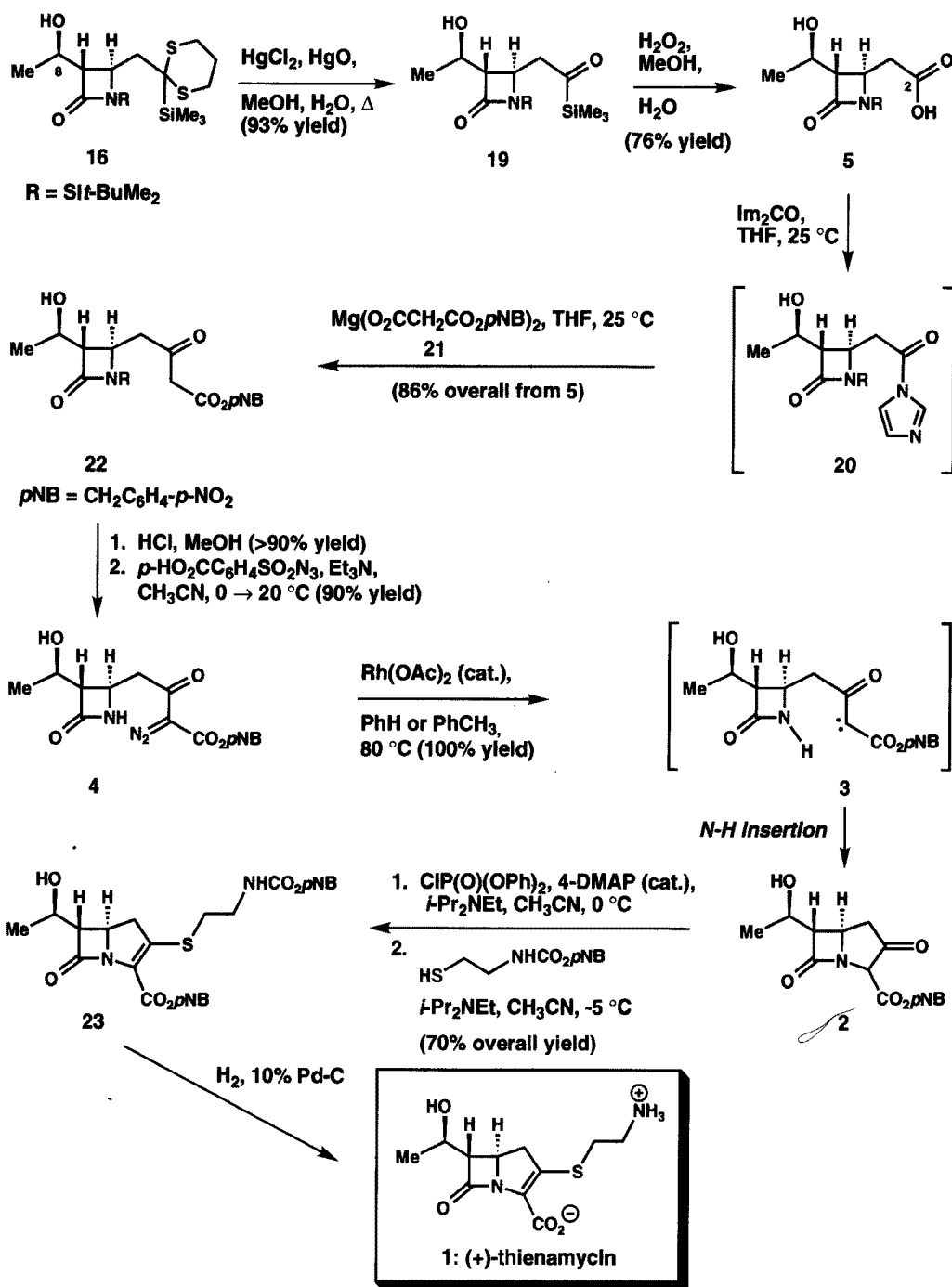




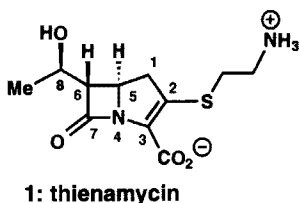
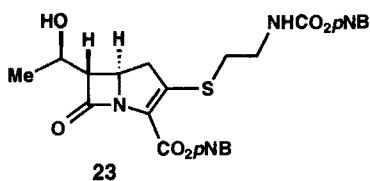
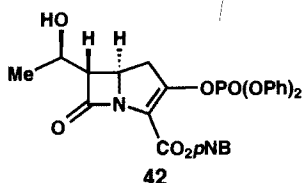
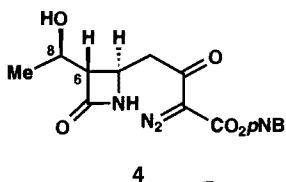
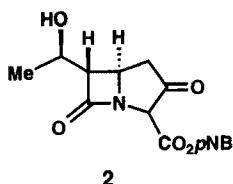
DMSO/triethylamine.¹⁰ It was recognized that a potential solution to the problem of establishing the (*R*) configuration at C-8 of thienamycin would be the diastereoselective reduction of a trigonal carbonyl group at C-8. Gratifyingly, the action of excess potassium tri-*sec*-butylborohydride (K-Selectride) and potassium iodide on intermediate **18** results in the formation of a 9:1 mixture of C-8 epimers in favor of the desired C-8 β -OH isomer **16**. The undesired C-8 epimer **17** could be recovered and converted back to **18** by oxidation. This two-step reaction sequence (**7** \rightarrow **18** \rightarrow **16**) provides an adequate and simple solution to the challenge presented by the C-6 side chain of thienamycin, and the contiguous stereocenters at C-6 and C-8. It should be noted at this point that the task of securing the correct absolute configurations at positions 5, 6, and 8 of thienamycin has been accomplished.

We are now in a position to address the elaboration of the C-5 side chain in **16** into a form suitable for the crucial cyclization event. Exposure of intermediate **16** to HgCl_2 and HgO in aqueous methanol results in hydrolysis of the dithiane moiety and furnishes acyl silane **19** in 93% yield (see Scheme 3). On warming in the presence of a slight excess of hydrogen peroxide in aqueous methanol, intermediate **19** is converted into carboxylic acid **5** in 76% yield after crystallization. To achieve the synthesis of thienamycin, it is obvious that a two-carbon chain must be appended to C-2 at some stage. Although the C-2 carboxyl group in **5** could conceivably be used to acylate a reactive organic nucleophile, its inherent acylating potential is low. It is, therefore, necessary to convert the carboxyl group of intermediate **5** into a more reactive carboxylic acid derivative. By way of a modification of Masamune's protocol,¹¹ **5** can be converted into imidazolide **20** with 1,1'-carbonyldiimidazole in THF at 25 °C. Imidazolide **20** is not isolated; it is treated directly with the magnesium salt of the mono *para*-nitrobenzyl ester of malonic acid (**21**), and is converted into β -keto ester **22** in 86% yield after decarboxylation. Removal of the *tert*-butyldimethylsilyl protecting group from the lactam nitrogen atom in **22** with methanolic HCl (>90% yield), followed by introduction of the diazo functionality with *para*-carboxybenzenesulfonyl azide (90% yield) affords the requisite cyclization substrate, intermediate **4**.

The diazo function in compound **4** can be regarded as a latent carbene. Transition metal catalyzed decomposition of a diazo keto ester, such as **4**, could conceivably lead to the formation of an electron-deficient carbene (see intermediate **3**) which could then insert into the proximal N-H bond. If successful, this attractive transition metal induced ring closure would accomplish the formation of the targeted carbapenem bicyclic nucleus. Support for this idea came from a model study¹² in which the Merck group found that rhodium(II) acetate is particularly well suited as a catalyst for the carbene-mediated cyclization of a diazo azetidinone closely related to **4**. Indeed, when a solution of intermediate **4** in either benzene or toluene is heated to 80 °C in the presence of a catalytic amount of rhodium(II) acetate (substrate:catalyst, *ca.* 1000:1), the processes



Scheme 3. Synthesis of (+)-thienamycin (1).



just outlined occur smoothly, and culminate in the formation of bicyclic β -lactam **2**. Although the bicyclic framework of intermediate **2** is highly strained, it is formed in quantitative yield from α -diazo keto ester **4**!

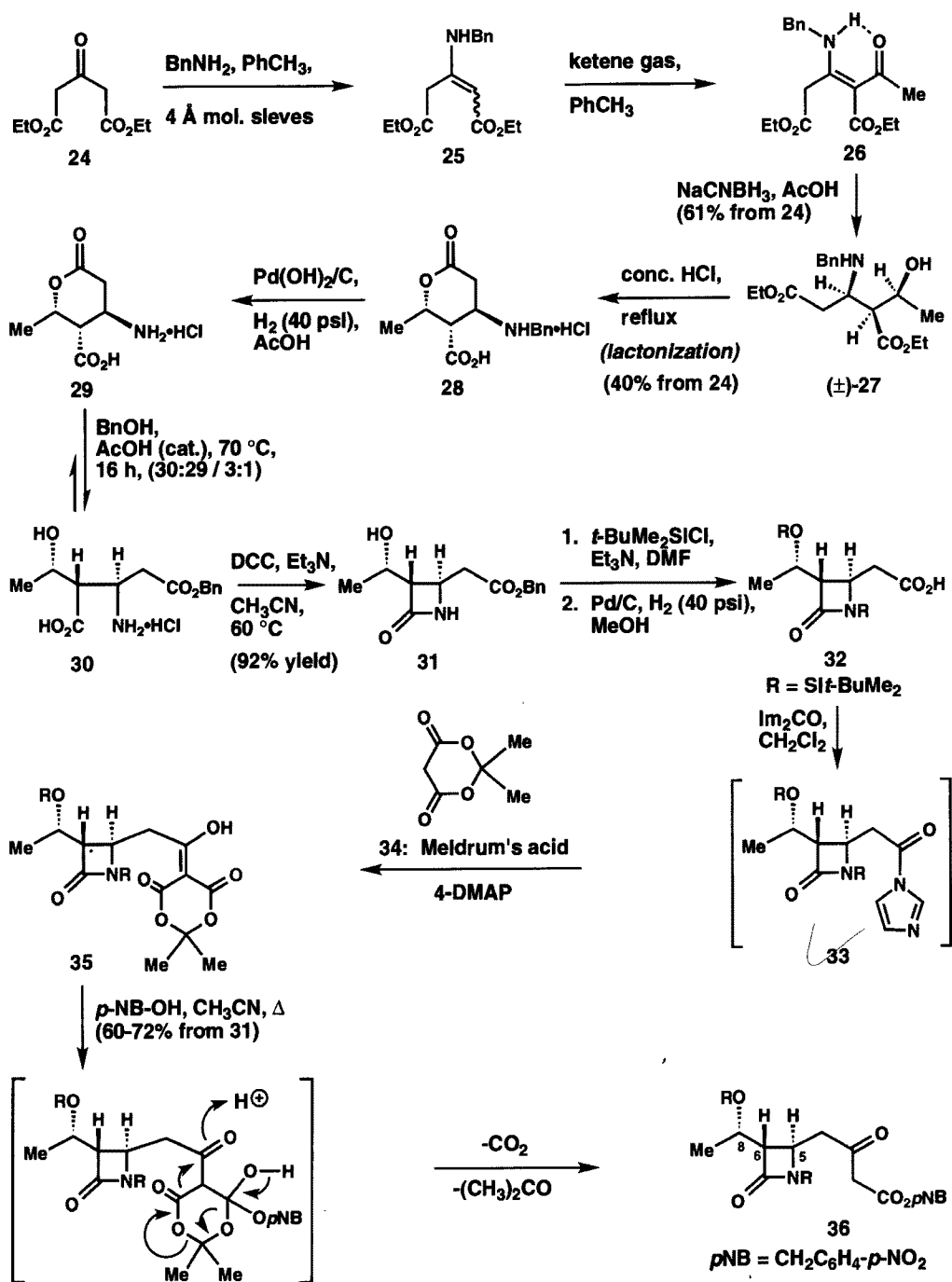
The β -keto ester moiety is a prominent structural feature of intermediate **2**. *A priori*, the keto function in **2** could suffer an attack by a thiol nucleophile to give, under dehydrating conditions, a vinyl sulfide. β -Keto esters can, however, exhibit a strong tendency to enolize, an event that would effectively attenuate the electrophilic character of the keto group. One might expect the β -keto ester moiety in **2** to exist largely in its enolic form, and it may be a simple matter to derivatize the enolic form of **2** in a manner that affords a more reactive electrophile. As it turns out, a bicyclic keto ester analogous in structure to compound **2** was found to exist exclusively in the keto ester tautomeric form.¹² Nevertheless, treatment of **2** with diphenyl phosphorochloridate, Hünig's base (*i*-Pr₂NEt), and a catalytic amount of 4-dimethylaminopyridine smoothly produces vinyl phosphate **42** which subsequently undergoes conversion to vinyl sulfide **23** upon exposure to *N*-[(*para*-nitrobenzyl)-oxycarbonyl] cysteamine (70% overall yield). The attack of the thiol nucleophile on the vinyl phosphate can be formulated as a Michael addition/elimination reaction.

The reactions that accomplished the conversion of intermediate **16** into intermediate **23** have taken place very smoothly. It is worth acknowledging that the β -hydroxy lactam moiety did not, at any stage, participate in any undesirable side reaction processes. The stability of the β -hydroxy lactam substructure in the presence of basic reagents is particularly noteworthy since a destructive retroaldol cleavage reaction could have conceivably occurred on several occasions. The stability of this potentially labile moiety permits all of the desired transformations leading from **16** to **23** to be conducted without prior protection of the C-8 hydroxyl group.

To complete the synthesis of thienamycin, it only remains to cleave the carbamate and ester functions in **23**. Catalytic hydrogenation of **23** accomplishes both of these objectives, and furnishes (+)-thienamycin (**1**). Synthetic (+)-thienamycin, prepared in this manner, was identical in all respects with natural thienamycin.

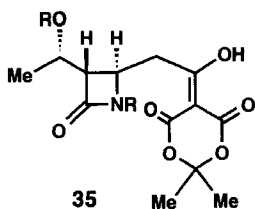
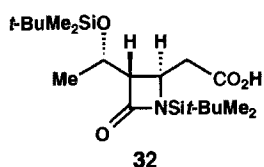
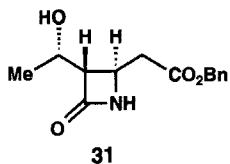
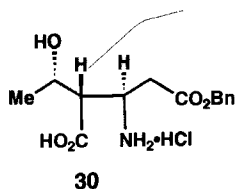
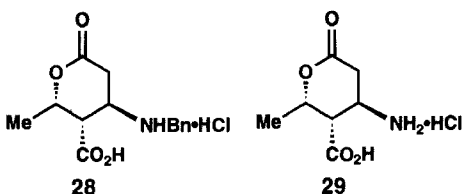
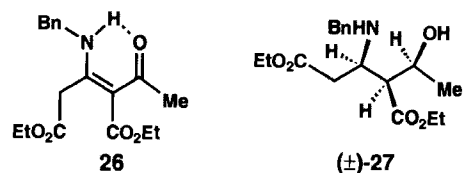
In 1980, a Merck group disclosed the results of a model study which amply demonstrated the efficiency with which the strained bicyclic ring system of thienamycin can be constructed by the carbene insertion cyclization strategy.¹² Armed with this important precedent, Merck's process division developed and reported, in the same year, an alternative route to carbene precursor **4**.¹³ Although this alternative approach suffers from the fact that it provides key intermediate **4**, and ultimately thienamycin, in racemic form, it is very practical and is amenable to commercial scale production. The details of this interesting route are presented in Schemes 4-6.

The starting material for this synthesis is diethyl 1,3-acetonedicarboxylate (**24**, Scheme 4), an inexpensive and commercially



Scheme 4. Synthesis of intermediate 36.

available substance. Treatment of a solution of **24** in toluene with benzylamine and molecular sieves results in the formation of enamine **25**. After filtration of the reaction mixture, treatment of the toluene filtrate with ketene gas accomplishes a smooth mono-*C*-acetylation of the nucleophilic enamine function in **25**, and provides keto enamine **26**. A salient and important feature of intermediate **26** is its intramolecular hydrogen bond. It was anticipated that this hydrogen bond would, by conferring conformational rigidity to **26**, permit the execution of a highly stereoselective reduction process. Indeed, exposure of **26** to sodium cyanoborohydride results in the diastereoselective reduction of both keto and enamine functions, and provides racemic **27** in an overall yield of 61 % from diethyl acetonedicarboxylate (**24**). For clarity, only the desired enantiomer is shown in Scheme 4. This simple reduction protocol creates three contiguous stereocenters from an achiral molecule. Although intermediate **27** can be purified by chromatography on silica gel, it is more convenient to lactonize it, and then purify the carboxylic acid that forms upon acid-induced hydrolysis of the ethyl ester function. Interestingly, the action of concentrated HCl on **27** at reflux accomplishes both of these objectives, and furnishes, after cooling of the reaction mixture, crystalline, diastereomerically pure lactone ammonium salt **28** in 40 % yield from **24**.



It is important to note that the one-step conversion of **27** to **28** (Scheme 4) not only facilitates purification, but also allows differentiation of the two carbonyl groups. After hydrogenolysis of the *N*-benzyl group (see **28** \rightarrow **29**), solvolysis of the δ -lactone ring in **29** with benzyl alcohol and a catalytic amount of acetic acid at 70°C provides a 3:1 equilibrium mixture of acyclic ester **30** and starting lactone **29**. Compound **30** can be obtained in pure form simply by washing the solid mixture with isopropanol; the material in the filtrate can be resubjected to the solvolysis reaction.

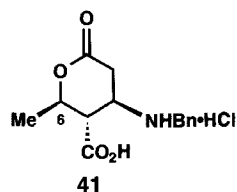
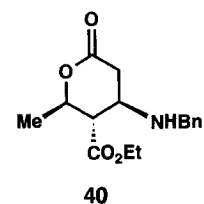
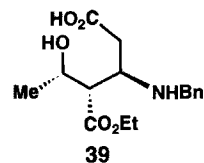
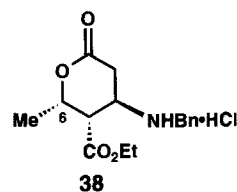
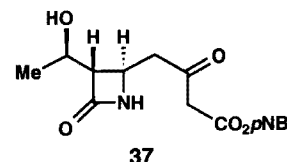
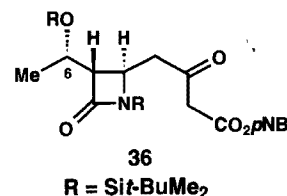
Intermediate **30** is depicted in a manner suggestive of a key transformation in this synthesis. Treatment of a solution of **30** in acetonitrile at 60°C with 1,3-dicyclohexylcarbodiimide (DCC) and triethylamine results in the formation of crystalline β -lactam **31** (92 % yield). In this step, DCC reacts with the free carboxyl group in **30** to give an activated ester which subsequently suffers an intramolecular attack by the primary amino group four atoms removed. Gratifyingly, β -lactam **31** can be obtained from this reaction in a form that is sufficiently pure for further advance. Thus, silylation of the β -lactam ring nitrogen atom and the C-8 hydroxyl group with *tert*-butyldimethylsilyl chloride, followed by hydrogenolysis of the benzyl ester, provides protected carboxylic acid **32**.

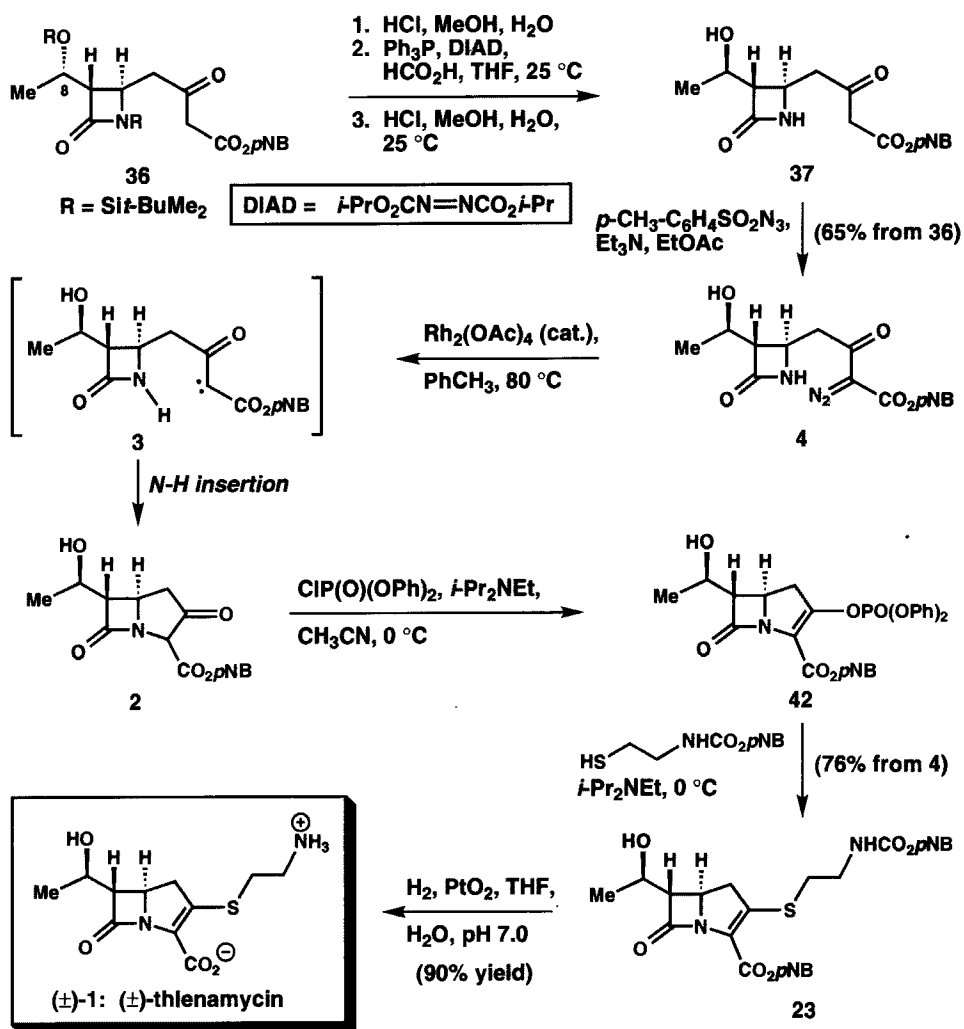
To set the stage for the crucial carbene insertion reaction, the acetic acid side chain in **32** must be homologated. To this end, treatment of **32** with 1,1'-carbonyldiimidazole furnishes imidazolidine **33**, a competent acylating agent, which subsequently reacts with the conjugate base of Meldrum's acid (**34**) to give **35**. Solvolysis of this substance with *para*-nitrobenzyl alcohol in acetonitrile at reflux provides β -keto ester **36** after loss of one molecule of ace-

tone and one molecule of carbon dioxide (see Scheme 4). This method for achieving the desired homologation is based on a known procedure.¹⁴ β -Keto ester **36** is easily purified by crystallization from isopropanol, and is obtained in 60–72% yield from **31**.

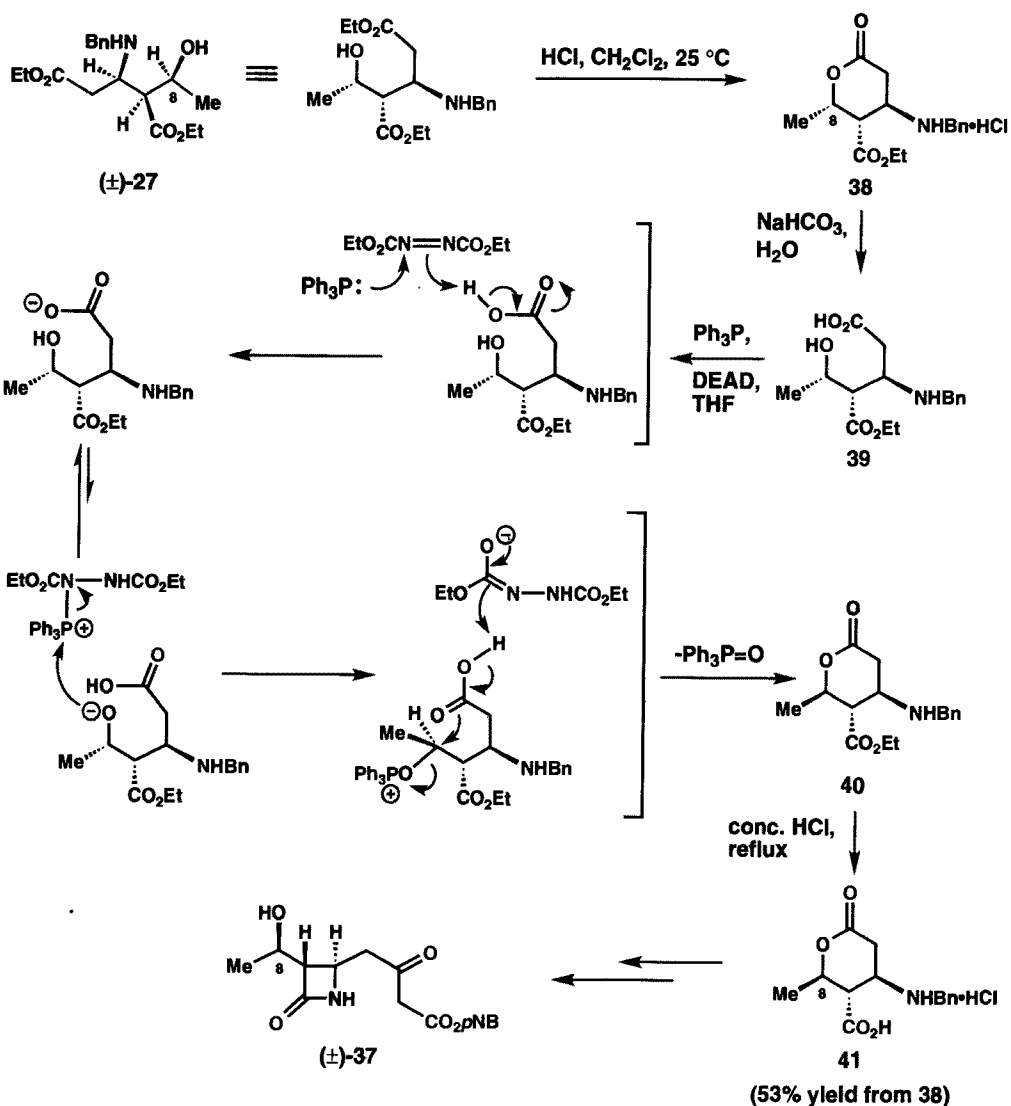
You will note that the relative stereochemical relationships between the three contiguous stereocenters in **36** do not match exactly those found in thienamycin. Although the *trans* disposition of the two side-chain appendages at carbons 5 and 6 in β -lactam **36** (Scheme 5) is correct, the configuration of the chirality center at C-8, relative to the other two, is incorrect. To secure correct relative stereochemical relationships, the errant configuration at C-8 must be inverted at some stage in the synthesis. When faced with the challenge of inverting the configuration of a hydroxyl-bearing stereocenter, one process that immediately comes to mind is the *Mitsunobu reaction*.¹⁵ After removal of the silyl protecting groups from **36** with HCl in aqueous methanol (see Scheme 5), subjection of the resultant secondary alcohol to a variant of the Mitsunobu reaction¹⁶ using triphenylphosphine, diisopropyl azodicarboxylate (DIAD), and formic acid results in the formation of secondary alcohol **37** after acid-induced hydrolysis of the inverted C-8 formate ester. It will be noted that the relative stereochemical relationships found in **37** now agree with those found in thienamycin.

As an alternative to the *intermolecular* Mitsunobu inversion strategy illustrated in Scheme 5, the Merck group subsequently described the use of an *intramolecular* Mitsunobu reaction to correct, earlier in the synthesis, the configuration of the C-8 hydroxyl-bearing stereocenter¹⁷ (see Scheme 6). Treatment of a solution of compound **27** in CH_2Cl_2 with anhydrous HCl at 25 °C induces lactonization and provides δ -lactone ester **38**. In contrast to the rather vigorous conditions employed to accomplish the conversion of **27** to **28** in Scheme 4, the action of HCl on **27** under anhydrous conditions at room temperature permits lactone ring formation without concomitant hydrolysis of the ethyl ester function. In spite of the presence of two potentially reactive carbonyl groups in compound **38**, selective hydrolysis of the newly formed lactone ring with one equivalent of sodium bicarbonate in water produces acyclic hydroxy acid **39**, and sets the stage for the key intramolecular Mitsunobu reaction. Interestingly, exposure of **39** to 1.3 equivalents each of triphenylphosphine and diethyl azodicarboxylate (DEAD) results in the formation of a new lactone, compound **40**, presumably through the processes illustrated in Scheme 6. During the course of the conversion of **39** to **40**, the configuration of the hydroxyl-bearing stereocenter is cleanly inverted. Although compound **40** can be purified by column chromatography, it is more convenient to hydrolyze the ethyl ester function with aqueous acid, and then to purify the resultant carboxylic acid ammonium salt **41** by crystallization from acetone (53% overall yield from **38**). Intermediate **41**, a diastereoisomer of **28**, can be transformed into **37** through a sequence of reactions that closely parallels the one illustrated in Scheme 4.¹⁷

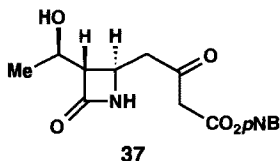




Scheme 5. Synthesis of (±)-thienamycin [(±)-1].



Scheme 6. Intramolecular Mitsunobu strategy for the inversion of the C-8 stereocenter (**39** → **41**).



Intermediate **37** can be transformed into (±)-thienamycin [(±)-**1**] through a sequence of reactions nearly identical to that presented in Scheme 3 (see **22** → **1**). Thus, exposure of β-keto ester **37** to tosyl azide and triethylamine results in the facile formation of pure, crystalline diazo keto ester **4** in 65 % yield from **36** (see Scheme 5). Rhodium(II) acetate catalyzed decomposition of **4**, followed by intramolecular insertion of the resultant carbene **3** into the proximal N–H bond, affords [3.2.0] bicyclic keto ester **2**. Without purification, **2** is converted into enol phosphate **42** and thence into vinyl sulfide **23** (76 % yield from **4**).¹⁸ Finally, catalytic hydrogenation of **23** proceeds smoothly (90 %) to afford (±)-thienamycin [(±)-**1**].

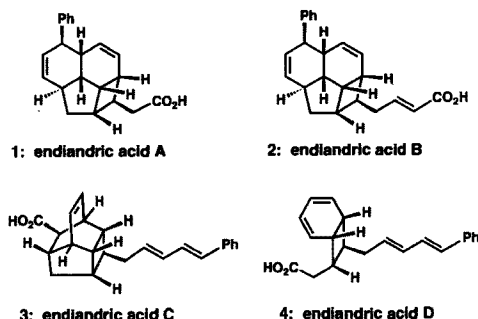
16.4 Conclusion

The unprecedented structure and potent antibiotic properties of thienamycin (**1**) motivated the development of many interesting synthetic strategies.^{19,20} In this chapter, we have witnessed two variants of a most elegant and conceptually novel approach to the synthesis of thienamycin. Both variants were developed by Merck scientists, and both feature the use of an intramolecular carbene insertion reaction²¹ to construct the strained bicyclic nucleus of the natural product. The development of this novel cyclization strategy can be traced to some earlier work at Merck which culminated in the synthesis of (±)-1-oxabisnorpenicillin G, a biologically active penicillin G analog.²² The synthesis of the latter substance has historical significance since it provides the first example of an intramolecular insertion of a carbenoid species into the N–H bond of a β-lactam.

The noteworthy successes of a relevant model study¹² provided the foundation for Merck's thienamycin syntheses. In the first approach (see Schemes 2 and 3), the journey to the natural product commences from a readily available derivative of aspartic acid; this route furnishes thienamycin in its naturally occurring enantiomeric form, and is noted for its convergency. During the course of this elegant synthesis, an equally impressive path to thienamycin was under parallel development (see Schemes 4 and 5). This operationally simple route is very efficient (>10 % overall yield), and is well suited for the production of racemic thienamycin on a commercial scale.

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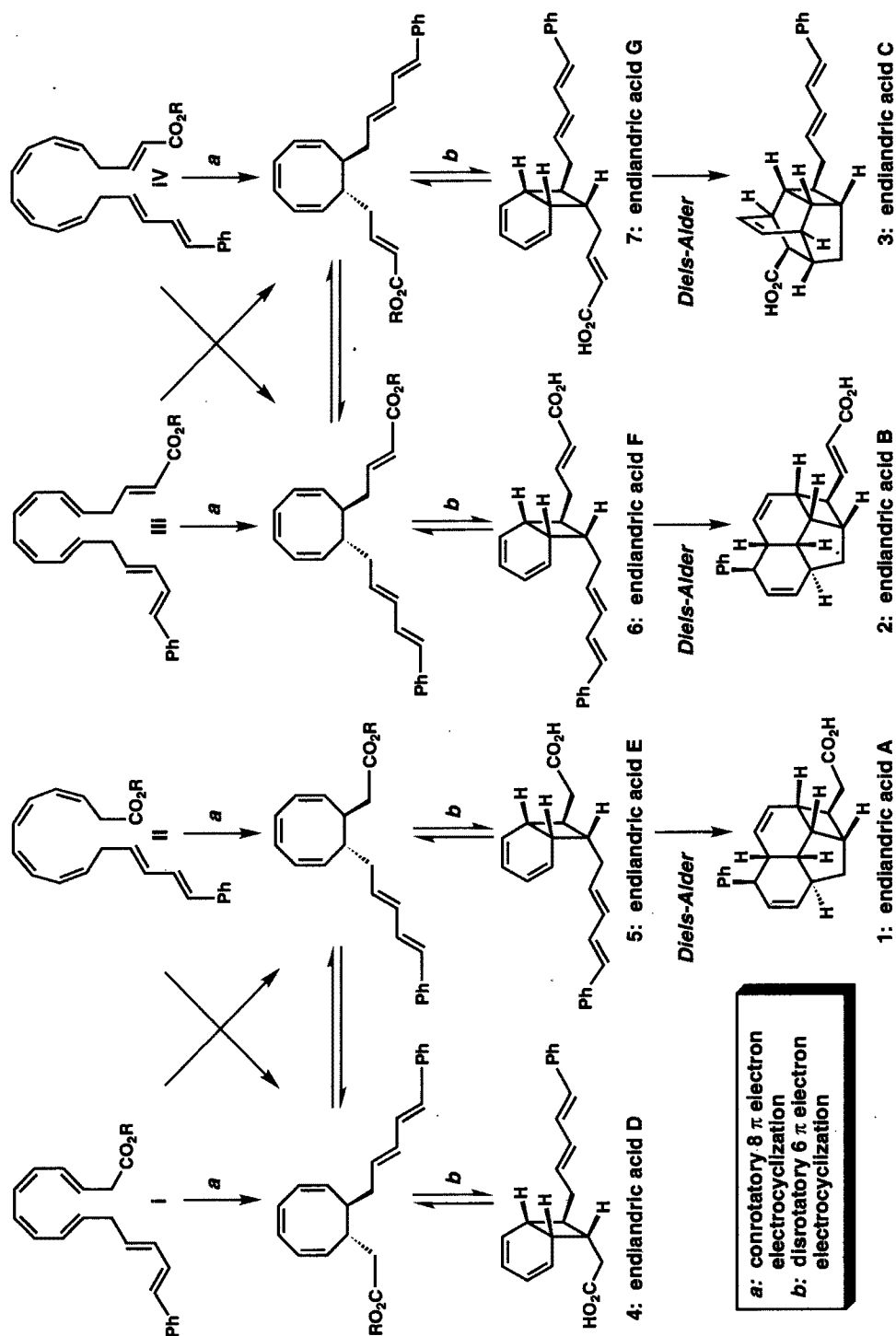
K. C. Nicolaou (1982)

Endiandric Acids A–D

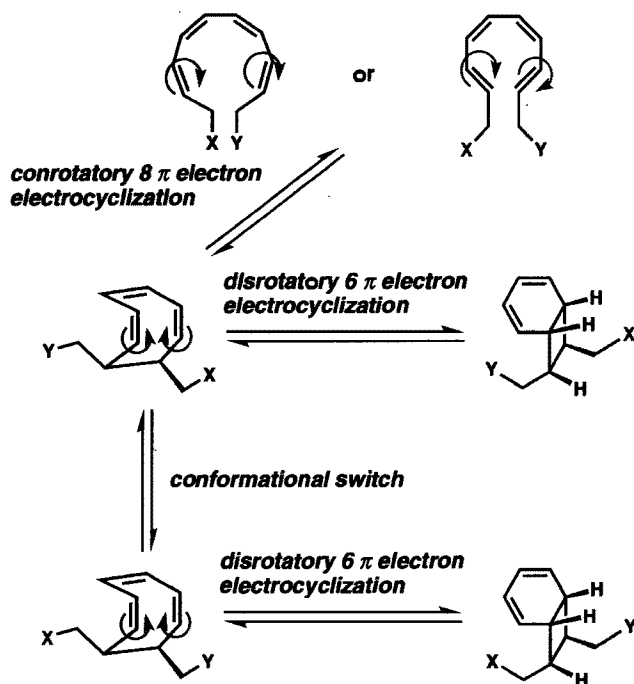
17.1 Introduction

The endiandric acids comprise a most notable class of secondary metabolites. Isolated in the early 1980s from the Australian plant *Endiandra introrsa* (Lauraceae) by D. St. C. Black's group,¹ these natural products are striking for their novel molecular architecture and their intricate structural interrelationships. Endiandric acids A (1), B (2), and C (3) contain four fused carbocyclic rings, a phenyl substituent and a carboxyl group. Despite containing eight stereogenic centers, the endiandric acids are found in nature as racemates, which is very unusual for chiral natural products. To explain this rather curious observation, Black proposed an intriguing hypothesis for the "biosynthesis" of these molecules from achiral polyunsaturated precursors through a series of *nonenzymatic* electrocyclizations (see Schemes 1 and 2). The Black hypothesis postulates the cascade of reactions shown in Scheme 1 as the pathway by which endiandric acids A–D are formed in nature. Thus endiandric acids E (5), F (6), and G (7) were proposed as immediate precursors to tetracyclic endiandric acids A (1), B (2), and C (3) respectively; the conversion being effected by an intramolecular Diels–Alder reaction. Endiandric acid D (4) cannot undergo an intramolecular Diels–Alder reaction, and so it does not form a corresponding tetracycle. An additional striking feature of the hypothesis of Black and coworkers is that endiandric acids D–G (4–7) could arise from sequential electrocyclizations of achiral polyenes I–IV through the intermediacy of 1,2-*trans*-disubstituted cyclooctatrienes (Scheme 1).

The molecular frameworks of the endiandric acids were unprecedented at the time of their discovery. Intrigued by these unique structures and Black's hypothesis for their biogenetic origin, the



Scheme 1. The endiandric acid cascade ($R = H, Me$).

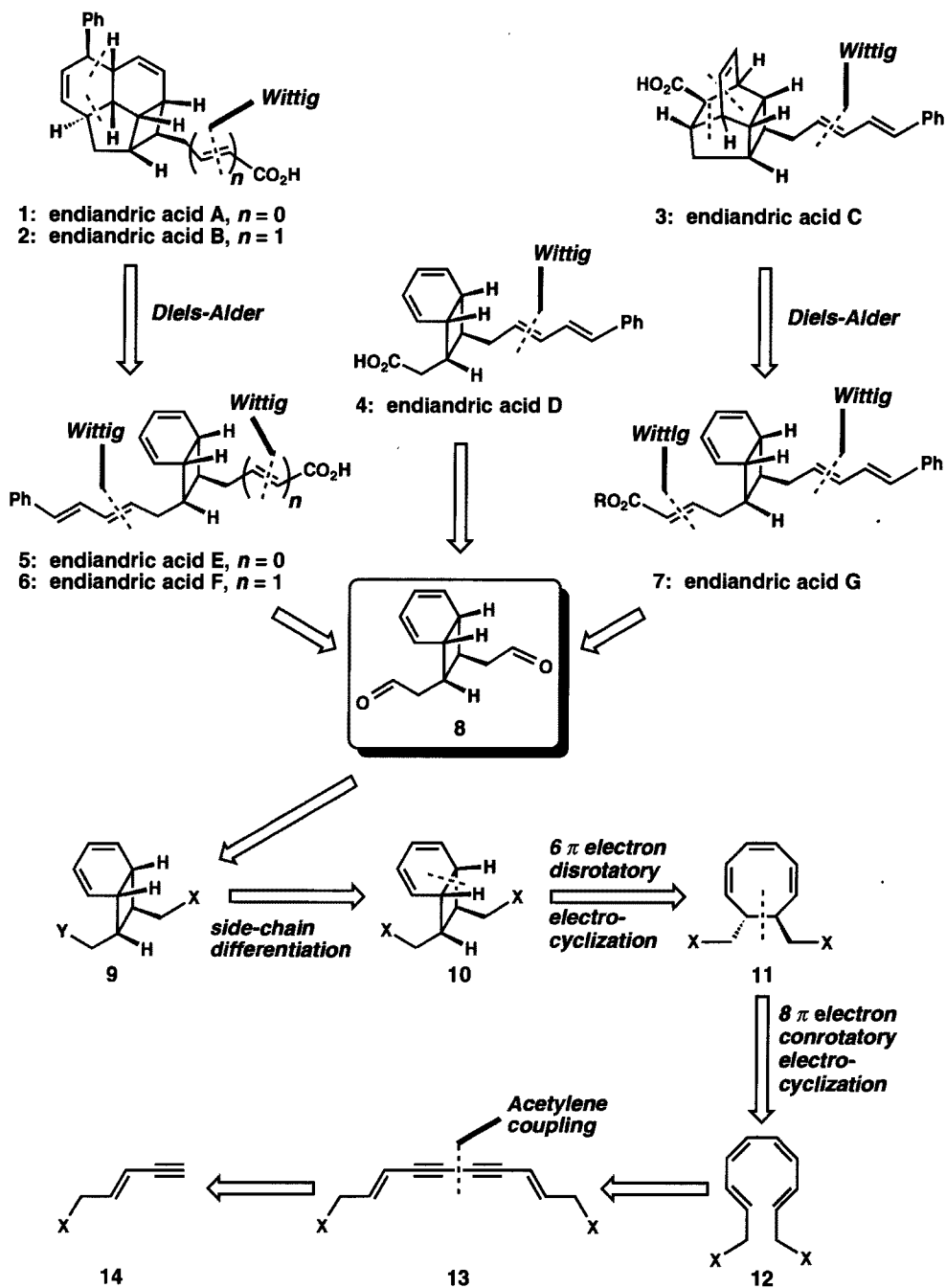


Scheme 2. Thermally allowed 8π electron and 6π electron electrocyclizations (Woodward–Hoffmann rules).

Nicolaou group initiated a program directed towards their total synthesis.²

17.2 Retrosynthetic Analysis and Strategy

The elegant and provocative biosynthetic hypothesis proposed by Black and coworkers guided the retrosynthetic analysis of the endiandric acids. The most logical and productive retrosynthetic disconnection of endiandric acids A (**1**), B (**2**), and C (**3**) appeared to be the one suggested by the biosynthetic hypothesis involving a retro Diels–Alder reaction as shown in Scheme 3. The forward transformation, the intramolecular Diels–Alder reaction, is, of course, well documented in the literature.³ A potential advantage of this strategy is that it leads to bicyclic endiandric acids E (**5**), F (**6**), and G (**7**). These compounds are closely related to a fourth endiandric acid unknown at the time of this planning, but anticipated to be a naturally occurring member of the family, namely endiandric acid D (**4**). Thus, the first subtargets became the four structu-



Scheme 3. Retrosynthetic analysis of endiandric acids A–G.

rally related endiandric acids D–G, all of which could conceivably arise from a common intermediate, dialdehyde **8** (Scheme 3) or its equivalent. Wittig-type or other olefination reactions would be required to achieve the construction of **4–7** from **8**. Differentiation of the two aldehyde functions in **8** would almost certainly be needed to achieve selectivity. Generalized intermediate **9** presents itself as a more practical precursor (one of the two substituents X and Y is an aldehyde and the other is a masked aldehyde). At this point, it was recognized that some degree of symmetry could be introduced into the precursor intermediates. Symmetry has always been a fascinating feature of many human endeavors, organic synthesis included. Symmetry can enhance the aesthetic appeal of a synthesis and can increase its efficiency, provided, of course, that differentiation of the symmetrical functionalities can be achieved at the appropriate point in the sequence. In the present case, intermediate **9** was considered as a differentiated derivative of compound **10**, a generic structure in which both appendages are terminated by the same group X. Two electrocyclization reactions operating on **10** in the retro direction lead to conjugated tetraene **12** via cyclooctatriene **11**. Further functional group manipulation provides **13** as a plausible precursor which, in addition to maintaining the same symmetry, is amenable to a direct synthesis from the commercially available enyne **14** (X=OH). In the synthetic direction, the conversion of intermediate **12** to the endiandric acids entails three tandem pericyclic reactions, two of which are electrocyclizations ($8\pi e^-$ and $6\pi e^-$) and one which is an intramolecular [4+2] cycloaddition. The two electrocyclic reactions are thermally allowed by the Woodward–Hoffmann rules⁴ and proceed in a stereospecific manner as shown in Scheme 2. Thus, in order to obtain the desired *trans* disubstituted [4.2.0] bicyclic product, the *trans/cis/cis/trans* or the *cis/cis/cis/cis* tetraenes must be used. When the two substituents (X and Y) are the same, the two bicyclic products are, of course, the same.

Although the above-mentioned electrocyclization reactions were well studied prior to the discovery of the endiandric acids, their utilization in the total synthesis of complex molecules had not been demonstrated. The endiandric acids, therefore, offered an irresistible opportunity to explore the utility of electrocyclization reactions in synthesis. The successful studies disclosed below demonstrate that these reactions can provide concise solutions to the challenge presented by complex polycyclic frameworks.

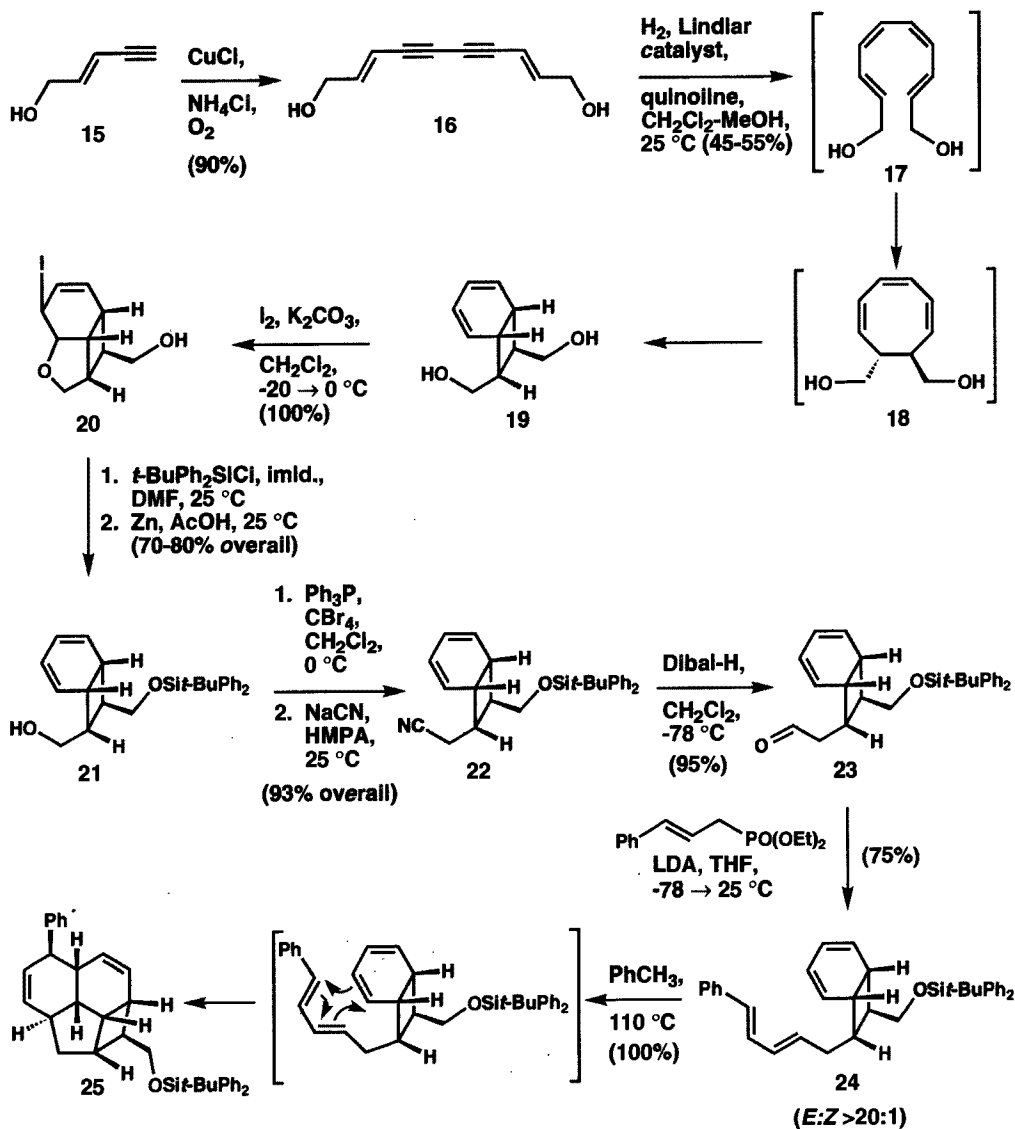
17.3 Total Synthesis

17.3.1 Stepwise, Stereocontrolled Total Synthesis of Endiandric Acids A–D (and E–G)

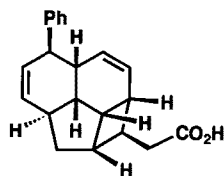
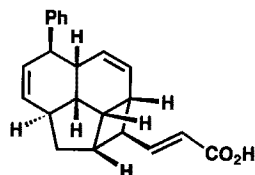
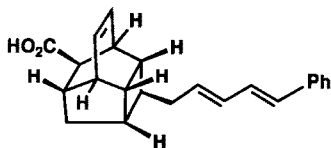
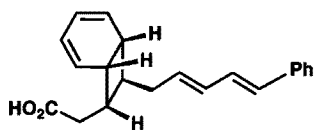
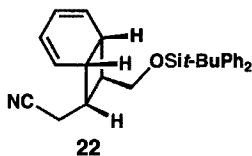
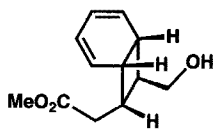
From the retrosynthetic analysis discussed above, a plan for a stepwise and stereocontrolled total synthesis of all the endiandric acids was evolved. The execution of the synthesis proceeded smoothly and delivered the target molecules efficiently and stereospecifically (see Schemes 4–7). Thus, subjection of commercially available *trans*-pent-2-en-4-yn-1-ol (**15**) to a classical Glaser acetylene coupling⁵ provides diacetylene **16** in 90 % yield (see Scheme 4). Partial hydrogenation of **16** (Lindlar catalyst, quinoline) results in the formation of tetraene **17**. The intermediacy of **17** is, however, only brief, for it participates in sequential $8\pi e^-$ conrotatory and $6\pi e^-$ disrotatory electrocyclizations to give bicyclic [4.2.0] system **19** in 45–55 % overall yield (see **17** → **18** → **19**). Unfortunately, the two hydroxyl groups in **19** could not be differentiated even with bulky reagents, and a special maneuver had to be devised for their sequential manipulation. You will note that the *endo*-oriented hydroxyl group in **19** resides in proximity to one of the π bonds in the six-membered ring. It was, therefore, anticipated that this unique spatial relationship could permit a facile iodoetherification reaction, thereby allowing a selective internal protection of the *endo* hydroxyl. Indeed, treatment of diol **19** with iodine and potassium carbonate provides, in quantitative yield, iodo ether **20**. Silylation of the remaining hydroxyl group in **20** with *tert*-butyldiphenylsilyl chloride under standard conditions, followed by reductive opening of the ether ring with Zn dust in acetic acid, gives the desired monoprotected hydroxy silyl ether **21** in 70–80 % overall yield from diol **19**. Treatment of alcohol **21** with CBr_4 and Ph_3P , followed by displacement of the resulting bromide with sodium cyanide in HMPA affords the nitrile **22** in 93 % yield. This nitrile (**22**) served admirably as a common intermediate for the stepwise and stereocontrolled total synthesis of all the endiandric acids (A–G).

The key intermediate **25** was prepared efficiently from aldehyde **23**, obtained by reduction of nitrile **22** with Dibal-H. Treatment of **23** with the lithium salt of *trans*-diethyl cinnamylphosphonate furnishes compound **24** in 75 % yield and with a 20:1 ratio of *E*:*Z* olefin stereoisomers. The stage is now set for the final and crucial operations to complete the molecular skeletons of endiandric acids A and B.

Gratifyingly, when compound **24** is refluxed in a solution of toluene at 110 °C, it undergoes quantitative [4+2] cycloaddition to polycyclic system **25**. The indicated stereochemistry of **25** was anticipated on the basis of the *trans,trans* geometry of the phenyl-diene system in precursor **24** and the presumed preference for an *exo* transition state geometry. These assumptions were vindicated by the eventual conversion of **25** to endiandric acids A (**1**) and B (**2**).



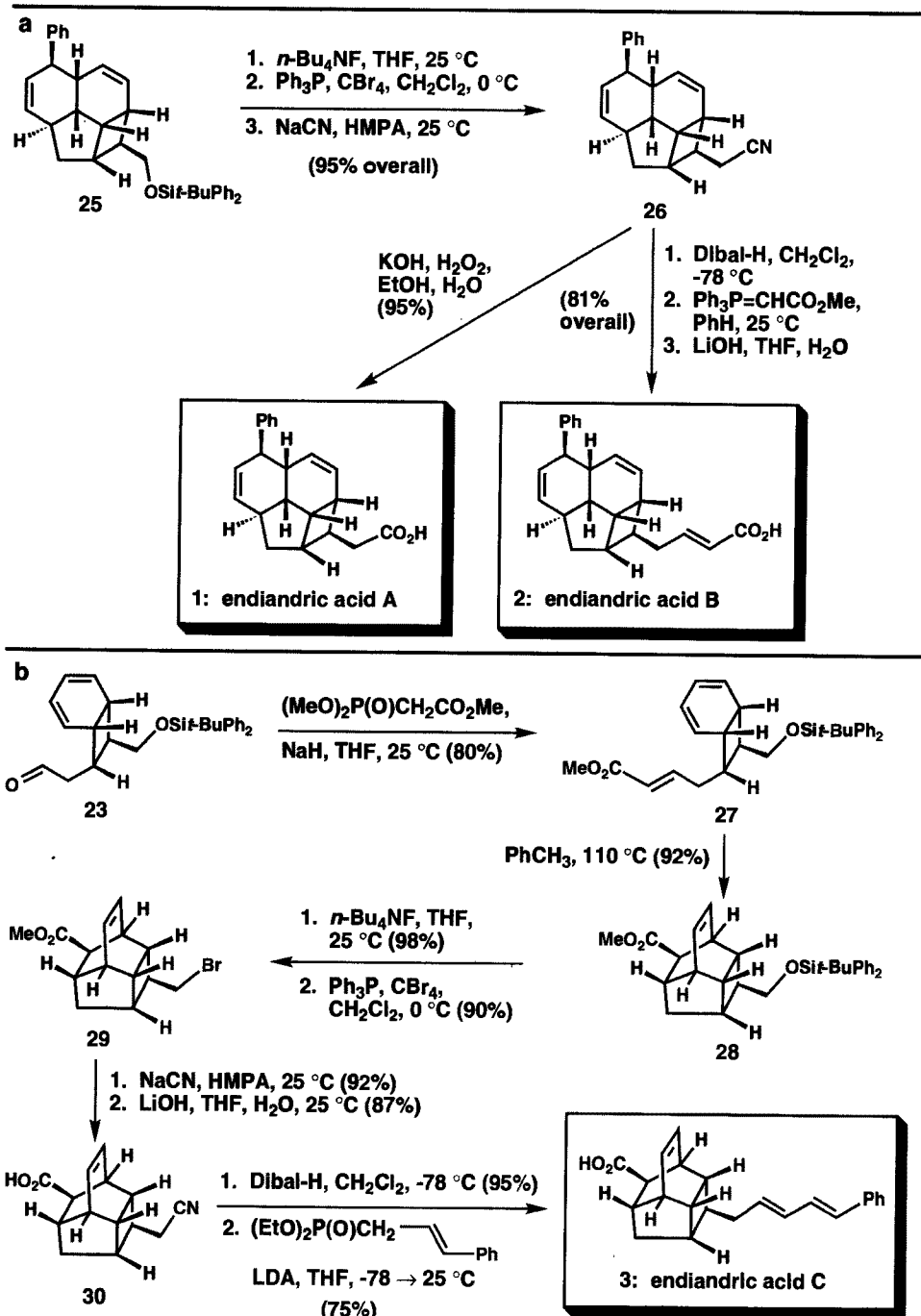
Scheme 4. Synthesis of intermediate 25.

**1: endiandric acid A****2: endiandric acid B****3: endiandric acid C****4: endiandric acid D****22****32**

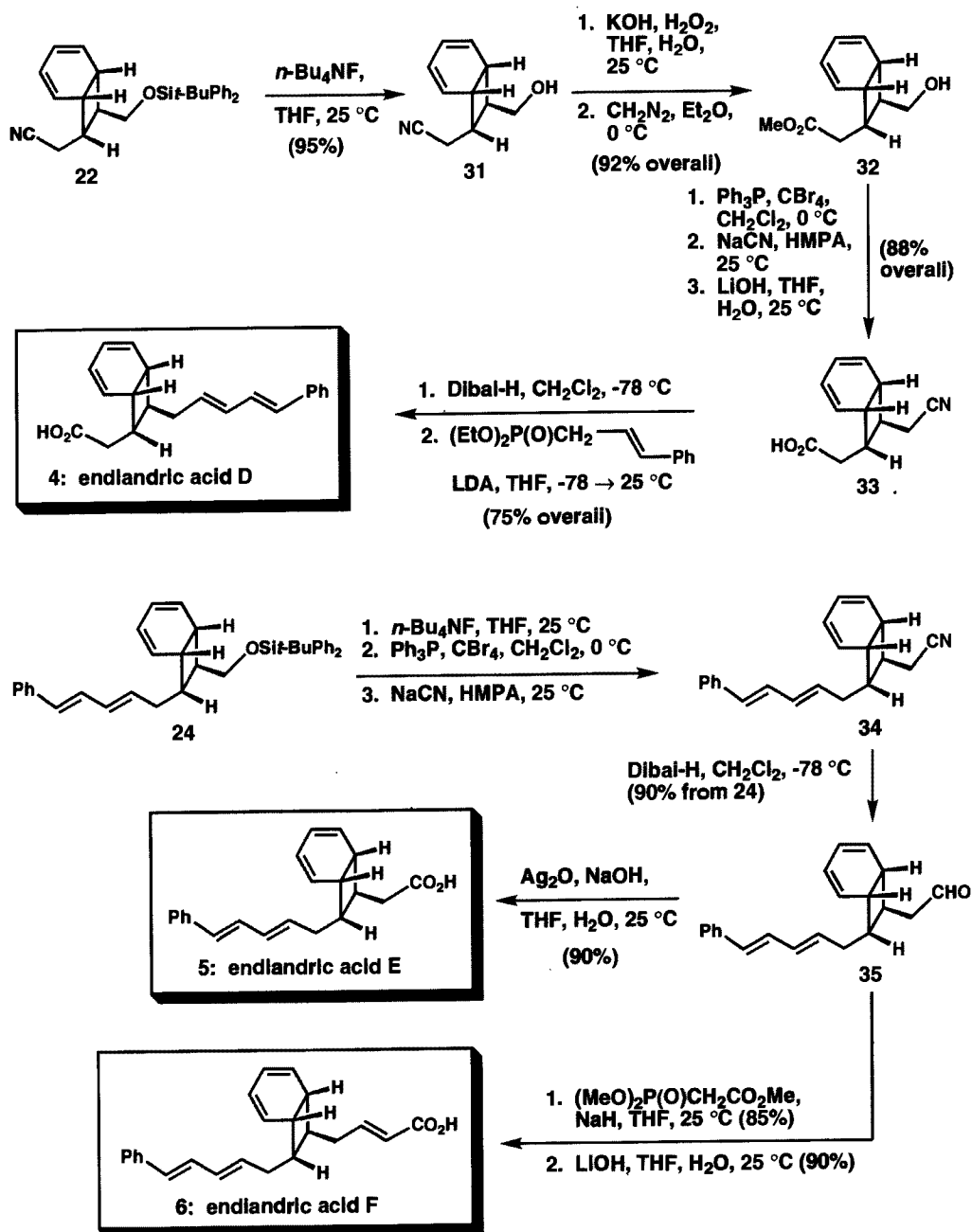
The final drive towards the target molecules proceeded as follows (see Scheme 5a). The silyl group is removed with fluoride ion and the resulting alcohol is converted to the corresponding bromide and then to the nitrile **26** (95 % overall yield). Finally, hydrolysis of the nitrile grouping in **26** with basic hydrogen peroxide at 25–50 °C furnishes, in 95 % yield, endiandric acid A (**1**). For the synthesis of endiandric acid B (**2**), nitrile **26** is taken through a different route. First, it is reduced with Dibal-H to afford the aldehyde which is then treated with $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ to afford the methyl ester of endiandric acid B in 81 % overall yield. Finally, endiandric acid B (**2**) was obtained from its methyl ester in quantitative yield by saponification with lithium hydroxide.

Endiandric acid C (**3**) can be synthesized from aldehyde **23** according to Scheme 5b. In contrast to the construction of endiandric acids A and B, only an isolated olefin is needed on the *endo* side chain of the molecule that can engage the 1,3-cyclohexadiene moiety in an intramolecular Diels–Alder reaction.³ Treatment of the anion derived from the action of sodium hydride on $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$ with aldehyde **23** gives, stereoselectively and in 80 % yield, the *E* α,β -unsaturated ester **27**. Refluxing compound **27** in toluene solution accomplishes the formation of the endiandric acid C framework **28** via the expected $[\pi 4_s + \pi 2_s]$ cycloaddition reaction in 92 % yield. Completion of the synthesis requires a series of steps by which the side chain on the cyclobutane ring can be homologated through an olefination reaction. Thus, desilylation of **28** with fluoride ion generates the corresponding alcohol (98 %) which can then be converted to bromide **29** by the action of $\text{Ph}_3\text{P}-\text{CBr}_4$ (90 %), and then to the corresponding nitrile by displacement of the bromide with cyanide ion (92 % yield). In order to provide protection for the carboxyl group during the impending Dibal-H reduction of the nitrile, the methyl ester is hydrolyzed to the corresponding carboxylic acid (**30**) with lithium hydroxide in 87 % yield. The reduction of **30** with excess Dibal-H proceeds smoothly in methylene chloride at low temperature and affords, upon workup, the desired aldehyde in 95 % yield. Finally, condensation of this substance with the anion derived from deprotonation of *trans* diethyl cinnamylphosphonate with LDA affords endiandric acid C (**3**) in 75 % yield.

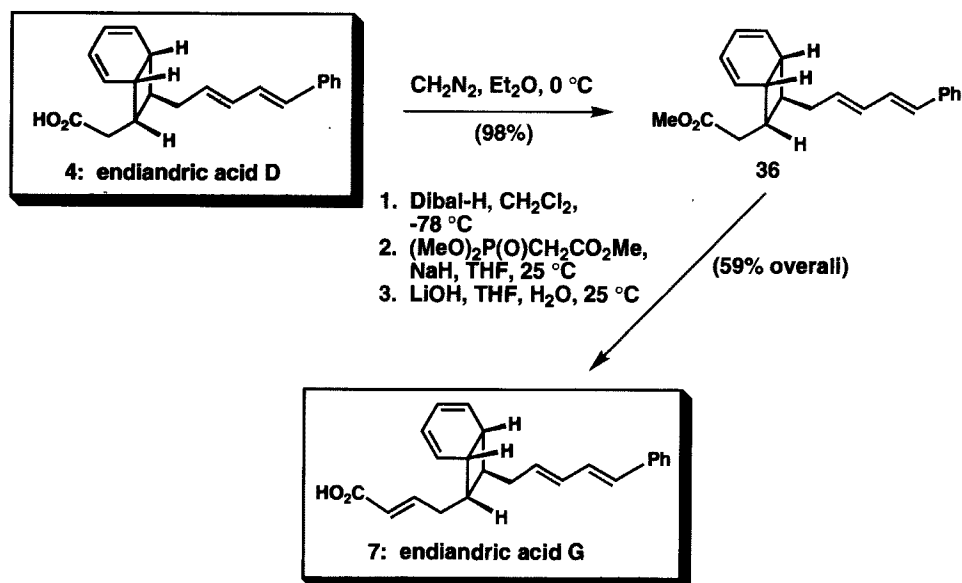
Although the “biosynthetic” cascade hypothesis predicts the co-occurrence of endiandric acids D (**4**) and A (**1**) in nature, the former compound was not isolated until after its total synthesis was completed in the laboratory (see Scheme 6). Our journey to endiandric acid D (**4**) commences with the desilylation of key intermediate **22** to give alcohol **31** in 95 % yield. The *endo* side chain is then converted to a methyl ester by hydrolysis of the nitrile to the corresponding acid with basic hydrogen peroxide, followed by esterification with diazomethane to afford intermediate **32** in 92 % overall yield. The *exo* side chain is then constructed by sequential bromination, cyanide displacement, ester hydrolysis (**33**), reduction, and olefination (**4**) in a straight-



Scheme 5. Syntheses of endiandric acids A (1) and B (2) (a), and C (3) (b).



Scheme 6. Syntheses of endiandric acids D (4), E (5) and F (6), and G (7).



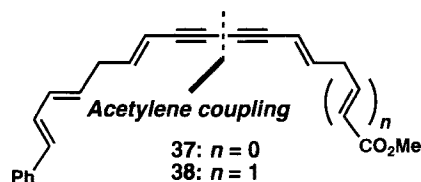
Scheme 6. Syntheses of endiandric acids D (4), E (5) and F (6), and G (7) (continued).

forward manner as already discussed for similar intermediates above.

The “biogenetic” scheme for endiandric acids also predicts the plausible existence in nature of endiandric acids E (5), F (6), and G (7). Even though they are still undiscovered, their synthesis has been achieved (Scheme 6). For endiandric acids E and F, key intermediate **24** is converted, by conventional means, to aldehyde **35** via intermediate **34**. Oxidation of **35** with silver oxide in the presence of sodium hydroxide results in the formation of endiandric acid E (5) in 90% yield, whereas elaboration of the *exo* side chain by standard olefination (85% yield) and alkaline hydrolysis (90% yield) furnishes endiandric acid F (6). The construction of the remaining compound, endiandric acid G (7), commences with the methyl ester of endiandric acid D (36) and proceeds by partial reduction to the corresponding aldehyde, followed by olefination and hydrolysis with aqueous base as shown in Scheme 6.

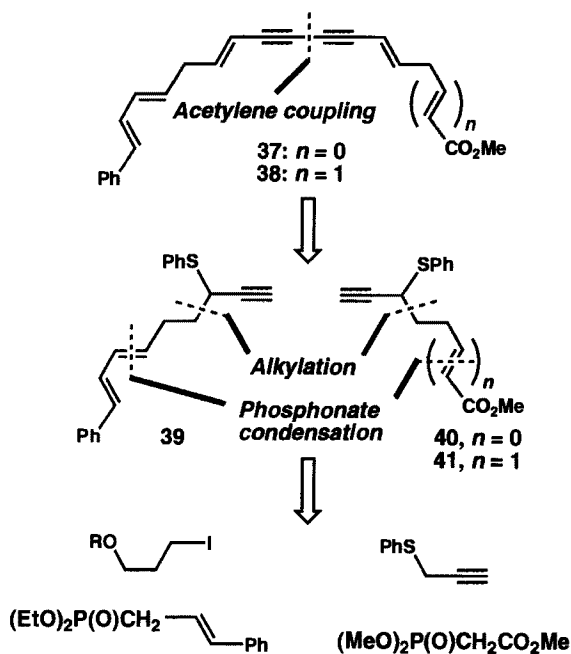
17.3.2 “Biomimetic”, One-Step Approach to Endiandric Acids A–D (and E–G)

Through a display of a series of electrocyclization reactions, the Nicolaou group demonstrated the “biomimetic”, one-step synthesis of the endiandric acids involving the cascade of reactions proposed by Black. The polyunsaturated compounds **37** and **38** (Scheme 7) were designed for their relative stability and potential to serve as

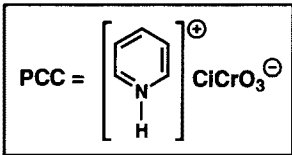


precursors to the required polyolefinic substances upon mild hydrogenation over Lindlar catalyst. Scheme 7 outlines, in retrosynthetic format, the general features of the strategy for the synthesis of these polyunsaturated molecules. Thus, disconnection of the carbon-carbon bond between the two acetylenic groups in **37** and **38** and functional group interchange by converting the two adjacent double bonds to single bonds carrying phenylthio groups leads to the terminal acetylenes **39–41**. In the synthetic direction, oxidation of sulfur to the corresponding sulfoxide followed by *syn*-elimination is expected to generate the desired *E* double bond in each compound. Two important reactions for carbon-carbon bond formation are then called upon to allow tracing of these intermediates (**39–41**) to simple starting materials as shown in Scheme 7. The use of heteroatoms (sulfur and phosphorus) in organic synthesis is amply demonstrated in these constructions. Alkylations of sulfur-stabilized anions and sulfoxide *syn*-eliminations are used to form, sequentially, single and double carbon-carbon bonds; phosphonate-aldehyde condensations are used to form olefinic bonds.

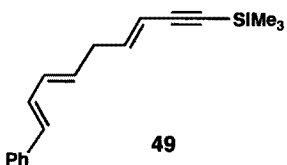
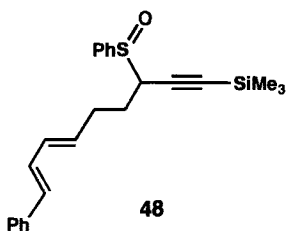
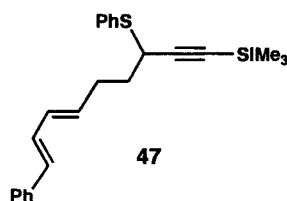
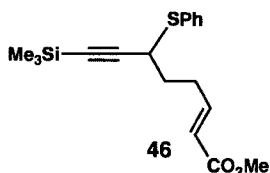
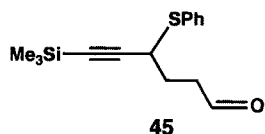
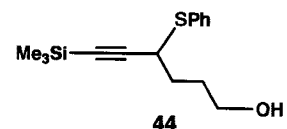
Scheme 8 summarizes the construction of the requisite building blocks **40**, **41**, and **50**. Alkylation of the lithio derivative of 1-(trimethylsilyl)-3-phenylthio-1-propyne (**42**) with 3-iodo-1-(*tert*-butyldimethylsilyloxy)propane in the presence of HMPA affords compound **43** in 90% yield. Selective desilylation of the protected alcohol is achieved by warming **43** to 40 °C in AcOH-THF-H₂O



Scheme 7. Retrosynthetic analysis of polyunsaturated precursors **37** and **38**.



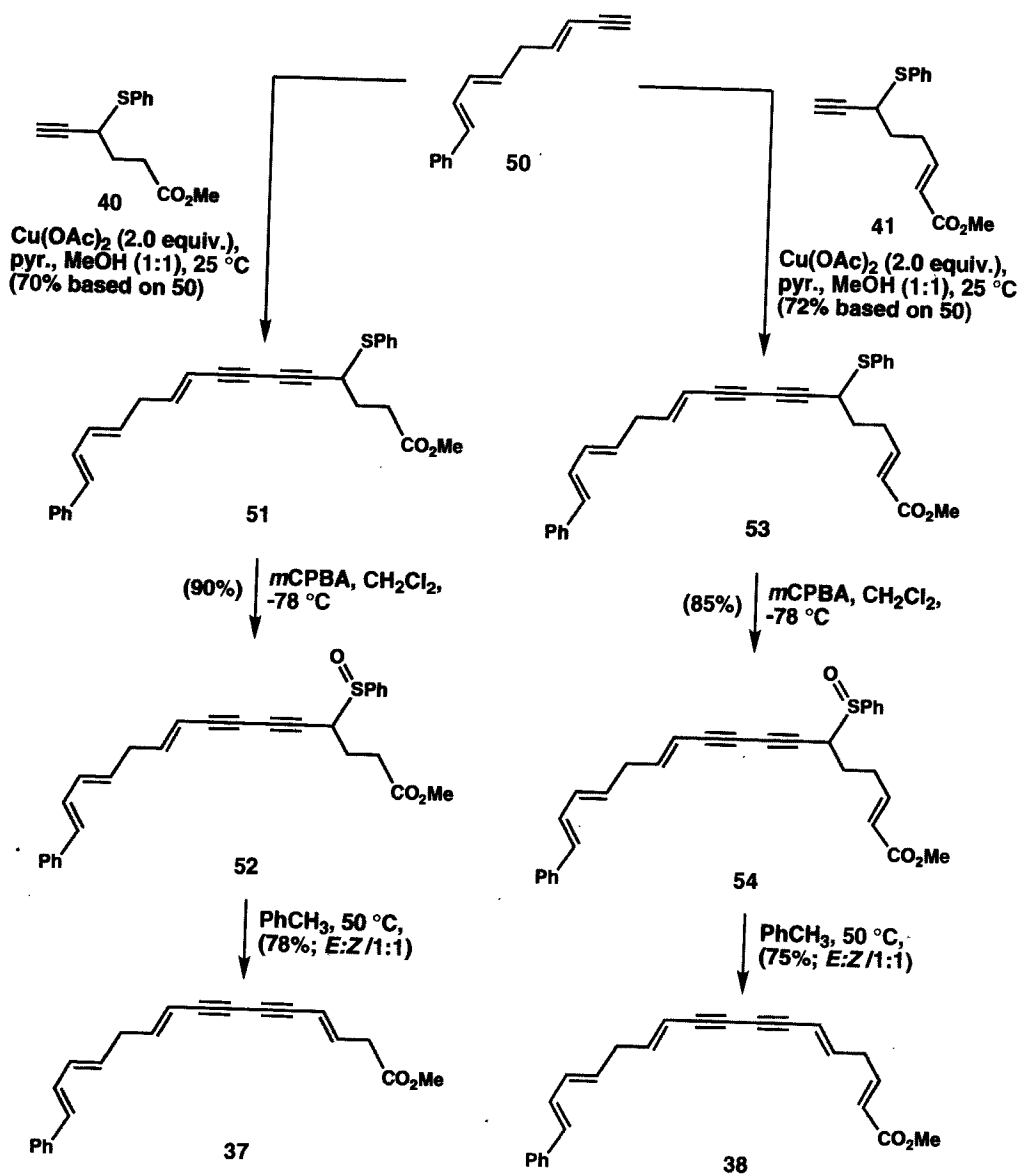
Scheme 8. Syntheses of intermediates **40**, **41**, and **50**.



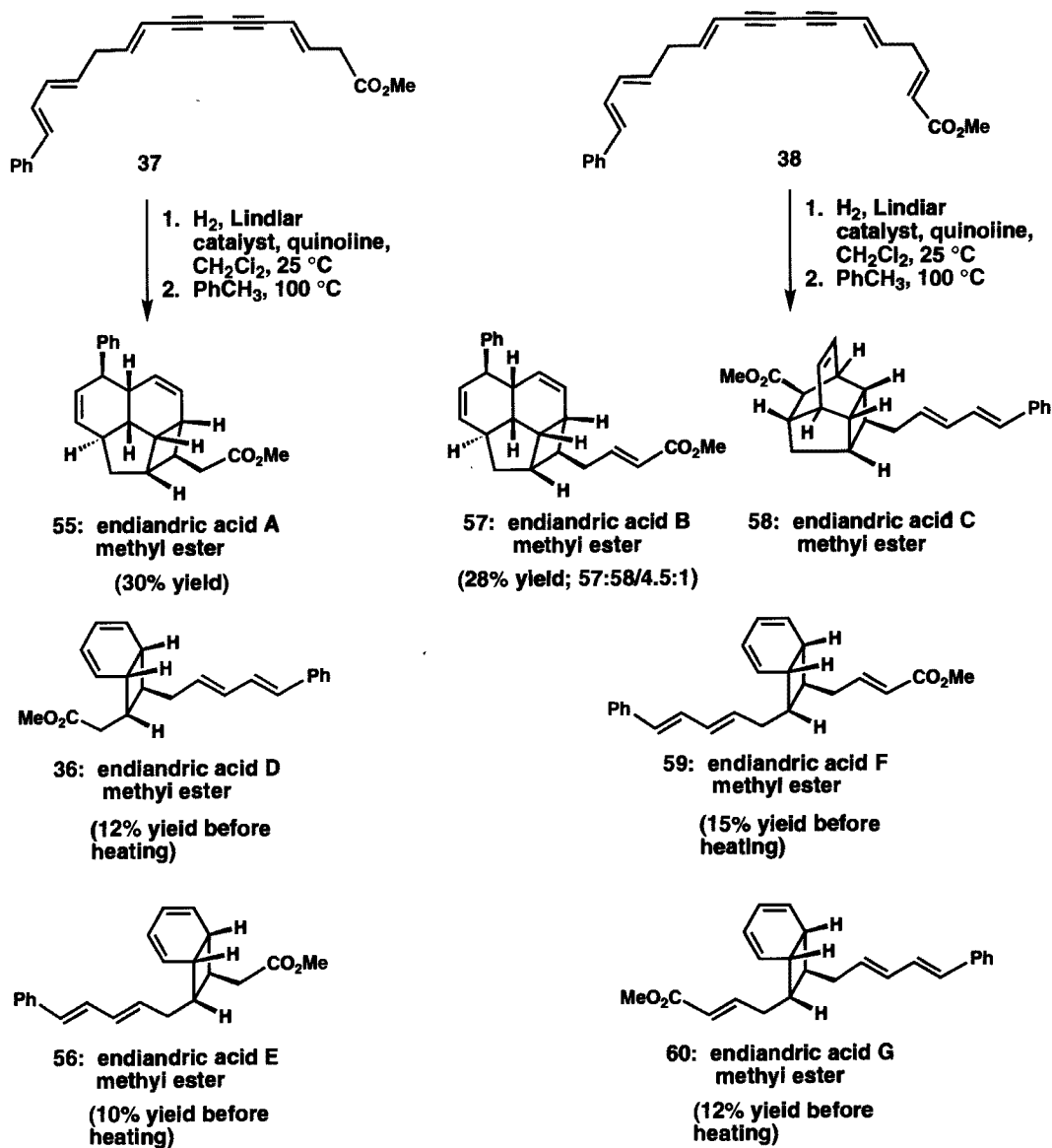
(3:2:2), affording alcohol **44** in 75 % yield. Jones oxidation of **44** to the corresponding carboxylic acid is possible under carefully controlled conditions leading, after esterification (CH_2N_2) and deprotection of the acetylene (KF/18-crown-6), to terminal acetylene methyl ester **40** in 68 % overall yield. Taken in a slightly different direction, primary alcohol **44** can be oxidized with pyridinium chlorochromate (PCC) in methylene chloride (76 %) or alternatively with $\text{SO}_3 \cdot \text{pyr}/\text{Et}_3\text{N}$ in DMSO (80 %) to the corresponding aldehyde **45**, a common precursor to both key intermediates **41** and **50**. Thus, standard olefination of **45** with the appropriate phosphonate reagent furnishes the *E* α,β -unsaturated methyl ester **46** stereoselectively and in 76 % yield. Finally, removal of the silyl group from **46** with fluoride ion results in the formation of terminal acetylene **41** in high yield. On the other hand, reaction of **45** with the appropriate cinnamyl phosphonate reagent produces, stereoselectively and in 78 % yield, diene **47**, the phenylthio group of which can be smoothly oxidized with *m*CPBA to afford the corresponding sulfoxide (**48**) in 98 % yield as a 1:1 diastereoisomeric mixture. The anticipated *syn*-elimination is accomplished when **48** is heated in a solution of toluene at 50 °C, furnishing a mixture of *E* and *Z* olefins (*ca.* 1:1) in 95 % total yield. The pure *E* isomer **49** can be desilylated with $\text{AgNO}_3\text{--KCN}$ in aqueous ethanol to afford the desired terminal acetylene **50** in 98 % yield.

With the required building blocks in hand, the targeted precursors **37** and **38** can be assembled as follows (see Scheme 9). A classical Glaser acetylene coupling reaction [$\text{Cu}(\text{OAc})_2/\text{pyr}\text{--MeOH}$] is utilized to join compound **50** with the more readily available **40** (five-fold excess), leading to diacetylene **51** in 70 % isolated yield (based on **50**). Selective oxidation of the sulfur atom in **51** with *m*CPBA affords the corresponding sulfoxide (**52**) as a mixture of diastereoisomers in 90 % total yield. Thermally induced *syn*-elimination introduces the necessary unsaturation leading to a mixture of *E* and *Z* geometrical isomers, in 78 % total yield, from which the pure *E* compound **37** is obtained after silica gel chromatography. In a similar fashion, and in similar yields, compound **38** can be synthesized from **50** and **41** (Scheme 9), setting the stage for the much anticipated triggering of the endiandric acid cascade and its experimental verification.

With the availability of suitable precursors, a systematic study of the endiandric acid cascade now became possible (see Scheme 10). The first experiment to be undertaken was the mild hydrogenation of the diacetylenic precursor **37** under carefully monitored conditions employing Lindlar catalyst and quinoline, followed by brief heating of the resulting mixture at 100 °C in toluene. Gratifyingly, it was possible to isolate endiandric acid A methyl ester (**55**) from this mixture in 30 % yield. The power of this cascade can only be fully appreciated when one recognizes that in a single operation, a simple achiral polyene is converted into the complex tetracyclic framework of endiandric acid A methyl ester with complete control over eight stereogenic centers! The apparent absence of endiandric



Scheme 9. Syntheses of intermediates **37** and **38**.



Scheme 10. “Biomimetic” syntheses of endiandric acids A–G.

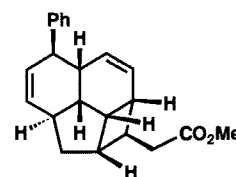
acid D methyl ester (**36**) in this reaction mixture is puzzling at first, but easily explained (and experimentally confirmed) on further reflection as discussed below. Examination of the reaction mixture in the above experiment *before heating* revealed the presence of both endiandric acids D and E methyl esters (**36** and **56**, respectively) which were isolated in 12 and 10% yields, respectively. Under these conditions, however, the conjugated tetraenes and cyclooctatrienes postulated in this cascade (see Scheme 1) were not observed, presumably due to their rapid conversion to the bicyclo [4.2.0] systems at ambient temperatures.

In a similar fashion, the selective hydrogenation of the extended diacetylene **38**, followed by brief heating at 100 °C, allowed the isolation of endiandric acid B methyl ester (**57**) and endiandric acid C methyl ester (**58**) in a combined yield of 28% and in a ratio of ca. 4.5:1 (see Scheme 10). Once again, in this remarkable sequence we witness the generation of the two seemingly unrelated and complex polycyclic structures of endiandric acids B and C by assembly of four new rings and eight stereocenters from a prochiral, open-chain precursor in a stereospecific manner. Endiandric acid F and G methyl esters (compounds **59** and **60**) respectively, could be isolated in ca. 15 and 12% yield, provided the complete operation was conducted at ambient temperature. As expected, the postulated conjugated tetraene and cyclooctatriene systems were not observed, apparently due to their rapid conversion to bicyclic compounds even at ambient temperatures (see Scheme 1).

With the demonstration of the pathways described above it became abundantly clear that the formation of endiandric acids in nature from polyunsaturated achiral precursors is quite feasible without the participation of enzymes, as Black had so insightfully suggested in 1980.

The kinetics of certain paths of this fascinating cascade were further studied by NMR spectroscopy. Thus, thermally induced transformations of the methyl esters of endiandric acids D–G were conveniently observed in $[D_8]$ -toluene at 70 °C by following the 1H NMR signal corresponding to the methyl ester group in these systems. Under these conditions, endiandric acid E methyl ester (**56**) was observed to undergo: (a) reversible isomerization to endiandric acid D methyl ester (**36**); and (b) irreversible intramolecular $[\pi 4_s + \pi 2_s]$ cycloaddition (Diels–Alder reaction) to endiandric acid A methyl ester (**55**) with a half-life ($t_{1/2}$) of ca. 1.3 h (at 70 °C) (Figure 1a). Eventually, all the material is transformed, and endiandric acid A methyl ester (**55**) is formed in high yield. Similar observations were made with endiandric acid D methyl ester (**36**) as shown in Figure 1b. Its half-life at 70 °C was determined to be ca. 3.8 h, endiandric acid A being formed essentially in quantitative yield. This finding explains the absence of endiandric acid D methyl ester (**36**) in the hydrogenation–thermolysis experiment discussed above.

The thermally induced reactions of endiandric acids F and G methyl esters (**59** and **60**) were followed in a similar fashion



55: endiandric acid A methyl ester

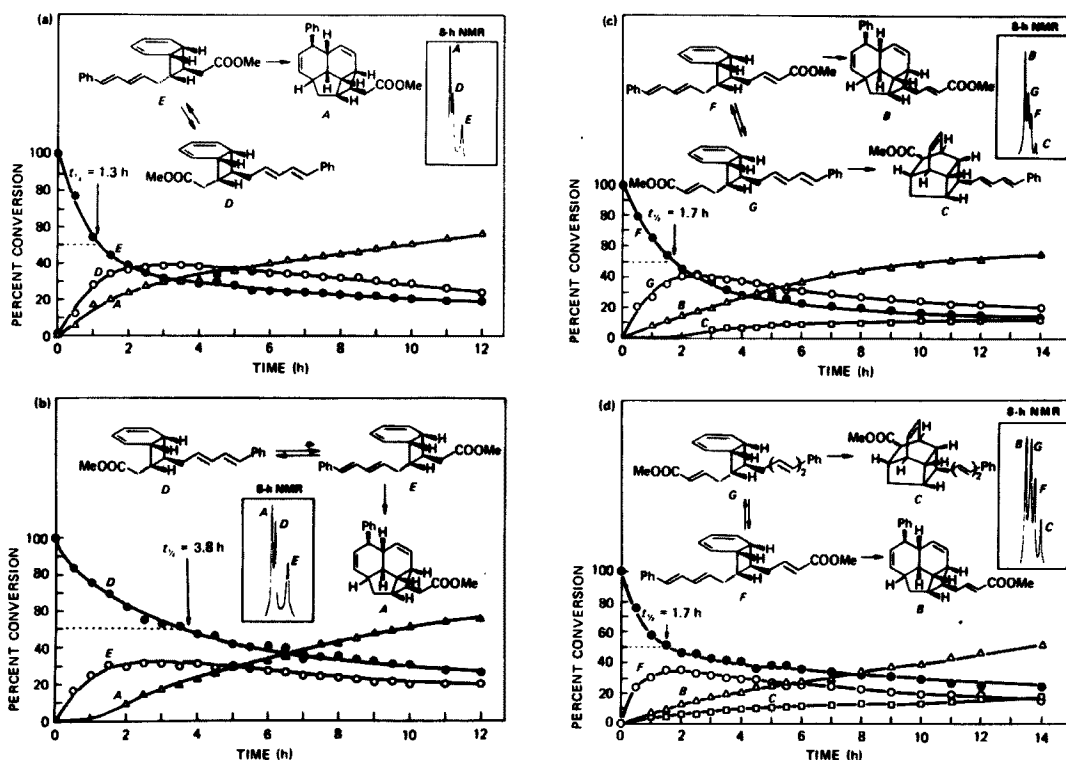
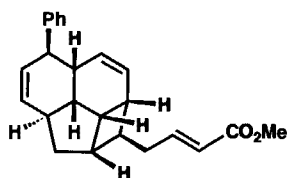
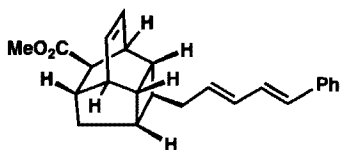


Figure 1. Thermolysis of the methyl esters of endiandric acids E (**56**) (a), D (**36**) (b), F (**59**) (c), and G (**60**) (d) at 70 °C in $[D_8]$ toluene. Data obtained by 1H NMR spectroscopy ($COOCH_3$) at 250 MHz. (from ref. 2d)



57: endiandric acid B methyl ester



58: endiandric acid C methyl ester

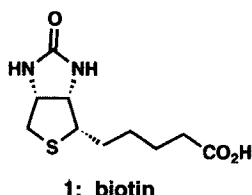
(Figure 1c,d). It was found that **59** and **60** are mutually interconvertible, and that both are eventually converted into compounds **57** (endiandric acid B methyl ester) and **58** (endiandric acid C methyl ester), respectively. Interestingly, compound G (**60**) was completely consumed with a half-life ($t_{1/2}$) of ca. 1.7 h (70 °C) producing endiandric acids B and C methyl esters (B and C) in a ratio of ca. 4.5:1, while compound F (**59**) was transformed to the same compounds (B and C, ca. 3.7:1 ratio) also in high yield and with a half-life ($t_{1/2}$) of ca. 1.7 h (70 °C). Apparently, the observed isomerizations $E \leftrightarrow D$ and $F \leftrightarrow G$ proceed by thermally allowed openings of the bicyclo[4.2.0] systems to cyclooctatriene systems, which undergo rapid conformational changes and reclose back to a mixture of the bicyclo[4.2.0] frameworks (see Scheme 1). It was, therefore, concluded by extrapolation of these results, that these chemical phenomena could take place in nature, albeit at slower rates.

17.4 Conclusion

The studies on the total synthesis of endiandric acids demonstrated a number of important principles of organic chemistry and provided experimental support for the rather daring hypothesis by Black regarding to their natural origin. Thus, the evolution of a highly challenging bicyclo[4.2.0] system by consecutive electrocyclizations ($8\pi e^-$ and $6\pi e^-$) demonstrates the power of such reactions in organic synthesis. The use of phosphonate condensation reactions proved quite powerful in constructing, in a stereocontrolled fashion, the required olefins, which provided the precursors to the final intramolecular [4+2] cycloaddition reactions *en route* to the target molecules. The "one-pot" construction of these targets through the endiandric acid cascade represents a remarkable and encouraging achievement in synthesis, particularly if one considers the stereospecificity of the chemical events which is, of course, encoded in the geometry of the double bonds involved in these remarkable, stereocenter-generating processes.

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Hoffmann-La Roche (1982)

Biotin

18.1 Introduction

In 1982, scientists at Hoffmann-La Roche disclosed an elegant, enantiospecific total synthesis of biotin (**1**).¹ Biotin (**1**) is an essential vitamin that functions as an indispensable coenzyme in a range of biocarboxylation reactions related to crucial physiological processes such as gluconeogenesis and fatty acid biosynthesis. Today, biotin is widely used in human nutrition and therapy, and in animal health. Although the biotin molecule is relatively small, its structure is interesting. Biotin (**1**) possesses three contiguous stereocenters, and its unusual tetrahydrothiophene ring accommodates a cyclic urea and a five-carbon-atom side chain terminating in a carboxyl group. The cyclic urea and the carboxylic side chain are oriented on the same side of the tetrahydrothiophene nucleus.

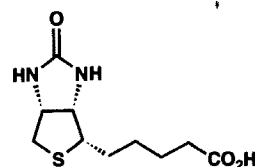
Several elegant synthetic strategies have been devised for biotin (**1**); this chapter describes one of the total syntheses developed at Hoffmann-La Roche. This insightful synthesis employs a derivative of L-cysteine, a readily available member of the chiral pool,² as the starting material, and showcases the powerful intramolecular nitron-olefin [3+2] cycloaddition reaction.

The class of 1,3-dipolar cycloadditions embraces a variety of reactions that can accomplish the synthesis of a diverse array of polyfunctional and stereochemically complex five-membered rings.³ The first report of a 1,3-dipolar cycloaddition of a nitron (a 1,3-dipole) to phenyl isocyanate (a dipolarophile) came from Beckmann's laboratory in 1890,⁴ and a full 70 years elapsed before several investigators simultaneously reported examples of nitron-olefin [3+2] cycloadditions.⁵ The pioneering and brilliant investigations of Huisgen and his coworkers⁶ have deepened our under-

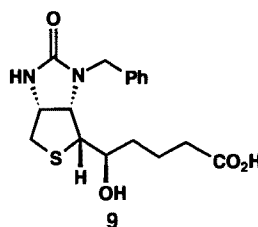
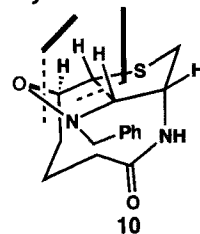
the first step. Significantly, nitron 4, an intermediate that is readily prepared from aldehyde 3, participates in a spontaneous intramolecular [3+2] cycloaddition reaction at room temperature to give a mixture of the desired all-*cis* cycloadduct 6 and the diastereomer 8 in excellent yield. This particular intramolecular nitron-olefin [3+2] cycloaddition reaction accomplishes the formation of a substituted tetrahydrothiophene ring and the creation of three new stereogenic centers, and it would appear to be particularly well suited for a total synthesis of biotin (1). Unfortunately, however, the ratio of 6 to 8 is only 1.9:1 and the situation is further complicated by the fact that cycloadducts 6 and 8 are both a mixture of diastereoisomers, epimeric at C-3. Thus, it was clear at a very early stage that an intramolecular nitron-olefin [3+2] cycloaddition reaction, in the structural context of 4, does not appear to constitute a viable strategy for a total synthesis of the biotin molecule.

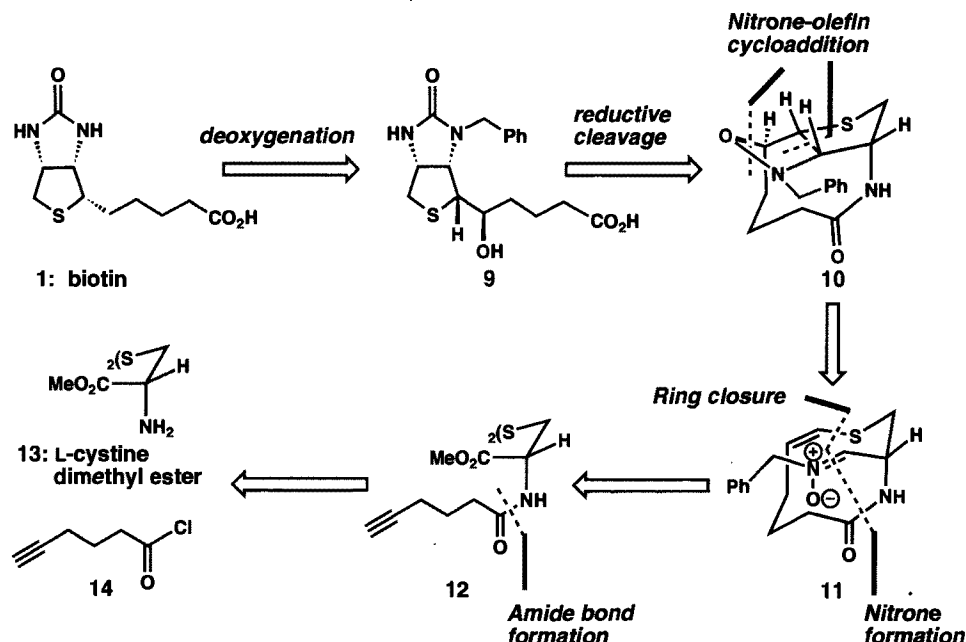
As we have seen, cycloadduct 6 is the major product formed in this reaction. The preferred formation of this stereoisomer was attributed to the guiding influence of an intramolecular hydrogen bonding interaction between the nitron oxygen and the urethane hydrogen on the course of the cycloaddition event (see 5, Scheme 1). It was reasoned that the hydrogen bond in 5 confers stability to this transition state geometry and guides the formation of [3+2] cycloadduct 6. This insight provided the foundation for the proposal that it should be possible to secure the formation of the desired [3+2] cycloadduct by enforcing the adoption of a transition state geometry that closely resembles 5. An important and elegant feature of this synthesis is the recognition that this objective could be achieved by confining the thioenol ether to a ten-membered ring. The use of rings as templates to achieve important synthetic objectives is a very important and general strategy in organic synthesis which is exemplified, in a particularly elegant way, by the Hoffmann-La Roche synthesis of biotin (1).

The Hoffmann-La Roche synthesis of biotin is outlined retrosynthetically in Scheme 2. Interestingly, the first retrosynthetic step actually introduces functionality. The introduction of a secondary hydroxyl group, and thus a new stereocenter, into structure 1 would appear to complicate the synthetic problem even further. In addition, "retrosynthetic simplification" of 9 affords intermediate 10, a predecessor which is even more structurally complicated than intermediate 9! It is certainly not obvious how the objective of synthesizing biotin (1) is being simplified on the basis of the first two retrosynthetic operations. However, the homology between intermediates 10 and 9 becomes very clear if we envision cleaving both isoxazolidine and lactam rings in 10. Reduction of the isoxazolidine N-O bond, in the synthetic direction, affords a hydroxyl group at one terminus and a free secondary amino group at the other, while cleavage of the lactam ring furnishes a carboxyl group at one end of the point of cleavage and a free primary amino group at the other. A straightforward functional group manipulation would then secure the formation of 9 from 10. Removal of the unwanted



1: biotin

Nitron-olefin
cycloaddition



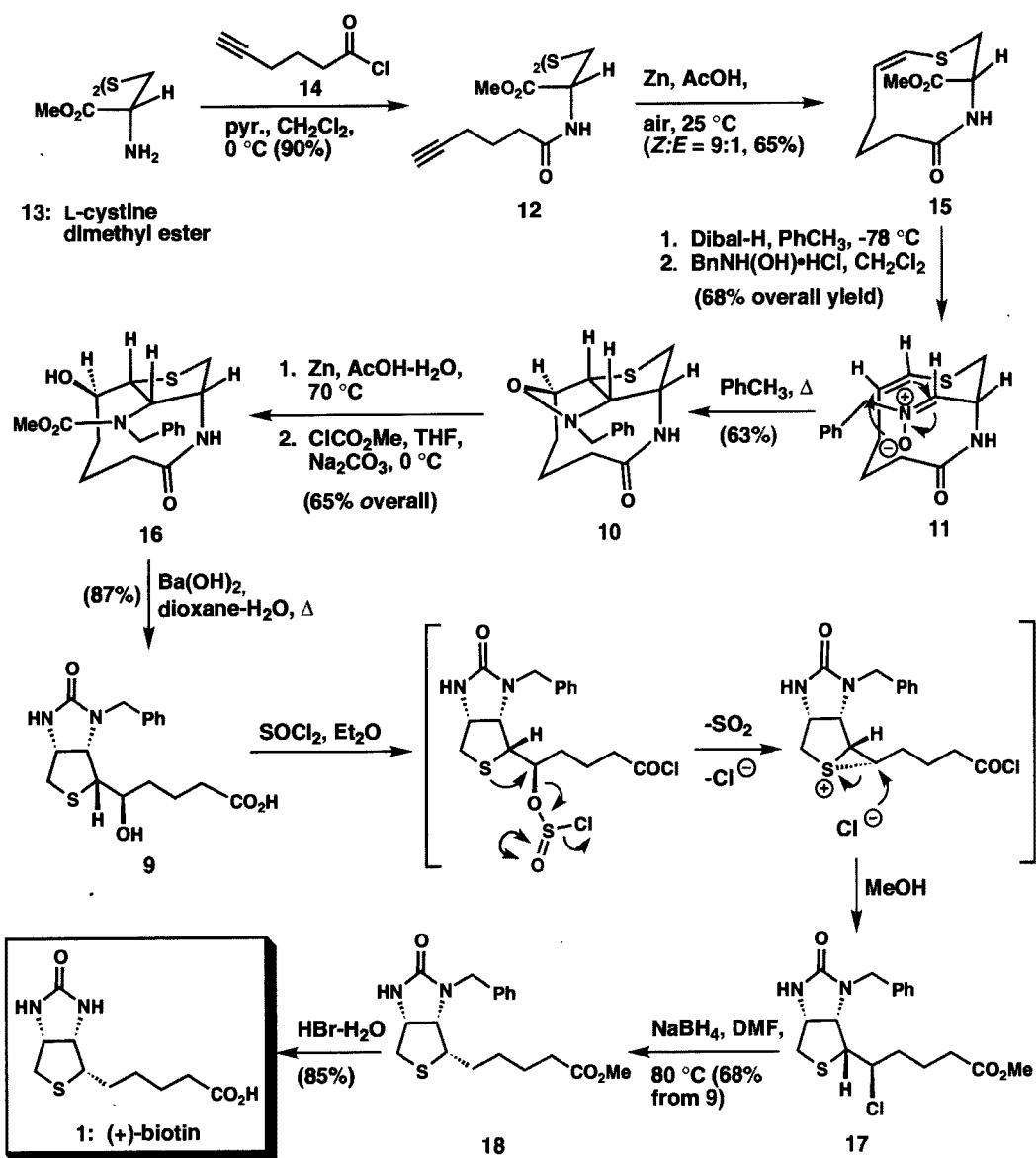
Scheme 2. Retrosynthetic analysis of biotin (**1**).

secondary hydroxyl group in **9** would complete the synthesis of biotin.

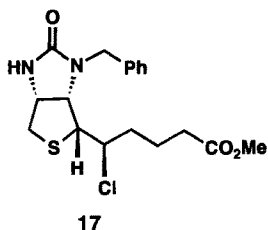
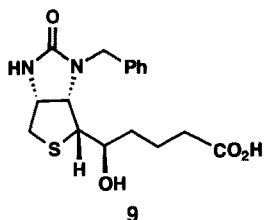
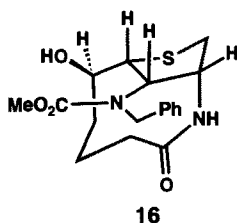
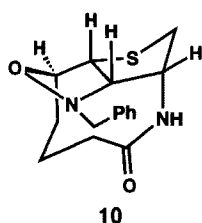
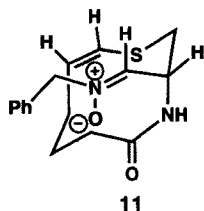
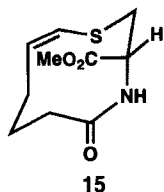
The isoxazolidine ring in intermediate **10** is a most important structural feature; its presence satisfies the structural prerequisite for the intramolecular nitron-olefin [3+2] cycloaddition transform.⁹ Cleavage of the indicated bonds in **10** furnishes nitron-olefin **11** as a potential precursor and key synthetic intermediate. It is in this retrosynthetic step that we witness significant structural simplification. In the forward sense, and in a single step, an intramolecular nitron-olefin cycloaddition reaction could convert intermediate **11**, a monocyclic compound which possesses one stereocenter, into intermediate **10**, a tricyclic molecule which is decorated with four contiguous stereogenic centers! By dismantling intermediate **11** in the indicated way, we arrive at **12** as a potential precursor. Cleavage of the amide bond in **12** provides L-cystine dimethyl ester (**13**) and acid chloride **14** as simple starting materials.

18.3 Total Synthesis

The synthesis commences with a straightforward acylation of the primary amino group of L-cystine dimethyl ester (**13**) with 5-hexynoyl chloride (**14**) to give amide **12** in 90% yield (see Scheme 3). The action of zinc dust in acetic acid on intermediate **12** accom-



Scheme 3. Synthesis of (+)-biotin (1).



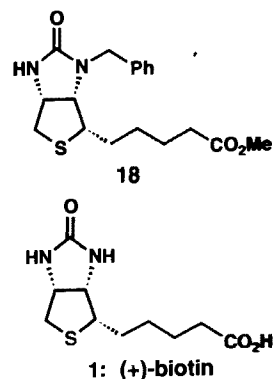
plishes the reduction of the disulfide bond and, if the reaction is carried out in the presence of air, the newly formed thiol reacts spontaneously with the terminal acetylene in an intramolecular fashion to give a 9:1 mixture of the *Z* ten-membered cyclic sulfide **15** and the corresponding *E* isomer in a yield of 65 %. A selective partial reduction of the methyl ester in **15** with diisobutylaluminum hydride (Dibal-H), followed by treatment of the newly formed aldehyde with benzylhydroxylamine hydrochloride, furnishes nitrone **11** in an overall yield of 68 %.

The stage is now set for the crucial intramolecular [3+2] cycloaddition. The tactic of forming the *Z* ten-membered cyclic sulfide is very significant because it restricts the mobility of the carbon-carbon double bond in space, and forces the ensuing intramolecular nitrone-olefin cycloaddition reaction to proceed through a transition state leading directly to the desired substituted isoxazolidine **10**. In the event, when a solution of **11** in toluene is heated at reflux, a smooth and stereospecific intramolecular cycloaddition takes place to give intermediate **10** in 63 % yield. In this impressive reaction, a new carbon-carbon bond is formed and three contiguous stereogenic centers are created, two of which will eventually be expressed in the final product. An X-ray crystallographic analysis confirmed the structure of **10**.

Reductive cleavage of the relatively weak N-O bond in **10** with zinc dust in aqueous acetic acid, followed by selective acylation of the secondary amine with methyl chloroformate, provides bicyclic intermediate **16** in an overall yield of 65 %. The ten-membered cyclic sulfide has played a crucial, but temporary, role in this synthesis. After having served its purpose of controlling the stereochemical course of the intramolecular [3+2] cycloaddition reaction, it is dismantled in a way that allows all of the carbon atoms of the connecting chain to be utilized in a productive fashion. Selective hydrolysis of the lactam in **16** with barium hydroxide in refluxing aqueous dioxane gives, after the nitrogen atom of the newly formed primary amino group attacks the proximal urethane carbonyl group, intermediate **9** in 87 % yield. The carbon atoms that formerly belonged to the ten-membered cyclic sulfide ring are now distributed between the tetrahydrothiophene ring and the alkane side chain, and both of these structural elements are found in the final product.

To complete the synthesis of biotin, all that remains is the removal of the nitrogen protecting group and the superfluous secondary hydroxyl group. When intermediate **9** is treated successively with thionyl chloride and methanol, chloro ester **17** is formed in 68 % yield. Interestingly, X-ray crystallographic analysis of **17** revealed that the secondary hydroxyl group in **9** was replaced by chloride with net retention of configuration. It is likely that anchimeric assistance by the tetrahydrothiophene sulfur atom in the reaction of **9** with thionyl chloride produces a transient episulfonium ion which subsequently reacts with chloride ion (Scheme 3).¹⁰ Of course net retention of stereochemistry should result under these circumstances. Reductive cleavage of the carbon-chlorine bond in

17 can be achieved easily with an excess of sodium borohydride to give intermediate **18** in 76 % yield. The action of aqueous hydrobromic acid on **18** accomplishes the concomitant removal of the benzyl protecting group and the hydrolysis of the methyl ester to give (+)-biotin (**1**) in a yield of 85 %. For convenience, (+)-biotin produced in this way was isolated and characterized as the corresponding methyl ester. The spectroscopic properties of synthetic (+)-biotin methyl ester were identical with those of the methyl ester prepared from natural biotin.

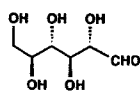


18.4 Conclusion

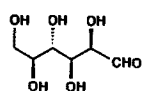
The total synthesis of biotin (**1**) described in this chapter provides an impressive example of the intramolecular nitron–olefin [3+2] cycloaddition reaction. Aiming for a practical process, the Hoffmann-La Roche group utilized relatively simple and inexpensive starting materials, and ingeniously controlled the crucial [3+2] cycloaddition reaction to give only one stereoisomer by confining the cycloaddition precursor to a ten-membered ring.

References

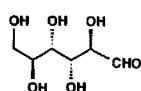
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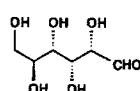
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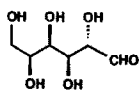
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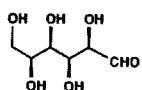
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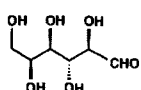
4: L-glucose



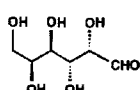
5: L-gulose



6: L-idose



7: L-talose



8: L-galactose

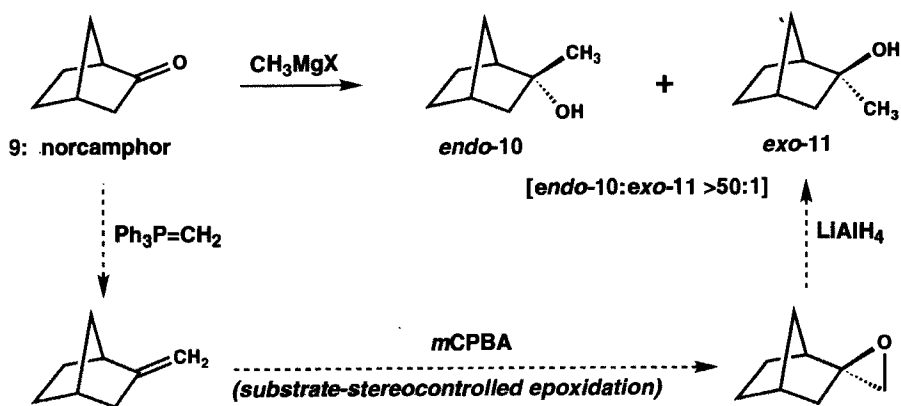
L-Hexoses

19.1 Introduction

"If carbonyl compounds have been said to be 'virtually the backbone of organic synthesis,' the epoxides correspond to at least 'one of the main muscles.'"¹ This informative metaphor offered by Professor Seebach acknowledges the important role of epoxides in organic synthesis. Indeed, epoxides are ubiquitous in organic chemistry; they are salient structural features of many natural products, and they constitute one of the most valuable classes of functional groups in organic synthesis.² By virtue of strain energy inherent in the three-membered oxirane ring, epoxides react readily with a wide variety of nucleophiles. It is important to note that epoxides possess two electrophilic carbon atoms, either one of which can participate in the formation of a bond with a suitable nucleophile. When presented with an unsymmetrical epoxide, a nucleophile thus has the option of reacting with two different sites. Nevertheless, it is often possible to control which epoxide carbon reacts with a nucleophile simply by controlling reaction conditions. For example, in basic media, a nucleophile will react selectively, in some cases exclusively, with the less sterically hindered epoxide carbon. In acidic media, on the other hand, a nucleophilic species can exhibit a strong preference for reacting with the more substituted (more hindered) carbon. In the latter case, the association of a protic or Lewis acid with the Lewis-basic epoxide oxygen affords an oxonium ion which seeks stabilization by withdrawing electron density from the carbon that can more easily accommodate electron-deficient character (i.e. the more substituted site); in the transition state, the nucleophile will react preferentially with the more electrophilic, more substituted, carbon.

Epoxides are conveniently formed through oxidation of alkenes, and a variety of oxidants can be used to accomplish this important transformation.² When a carbon-carbon double bond is present in a molecule that contains one or more stereocenters, the two faces of the olefin are usually diastereotopic. Provided that the resident stereocenter(s) and the double bond are in reasonable proximity, it is often possible to achieve a diastereoselective epoxidation. The stereochemical course of the epoxidation reaction is thus guided by preexisting asymmetry in the substrate molecule, and the stereocenter(s) produced in the epoxidation reaction bear a specific relationship to those already present in the substrate (relative asymmetric induction).³ This is the essence of the *substrate-control* strategy for the achievement of stereochemical control. It is instructive to note that prior to the 1980s synthetic chemists relied extensively on a substrate's unique structural features to achieve stereochemical control, and many ingenious, albeit substrate-specific, solutions to stereochemical problems have been recorded using this traditional strategy. Indeed, some of the most spectacular achievements in organic synthesis feature the substrate-control paradigm.

The diastereoselective addition of CH_3MgX to norcamphor (**9**) constitutes a simple, yet instructive, example of substrate control over the introduction of a new stereocenter (see Scheme 1).^{4,5} In this example, the action of methyl Grignard reagent on **9** results in the formation of a >50:1 mixture of *endo*- and *exo*-alcohol diastereoisomers in favor of *endo*-alcohol **10**. The biased geometry of norcamphor (**9**) enforces an *exo*-selective addition of the Grignard reagent to the ketone carbonyl. To be more precise, norcamphor (**9**) is a chiral molecule and the two faces of its keto function are diastereotopic. As a result, the transition state for the addition of CH_3MgX to the less crowded *exo* diastereoface is of lower energy, resulting in the preferential formation of *endo*-alcohol **10**. This is



Scheme 1. Substrate-controlled diastereoselection.

an example of asymmetric induction through substrate control because preexisting chirality in **9** controls the stereochemical course of the reaction producing the new stereocenter.

As simple as the example in Scheme 1 may be, it does highlight a fundamental weakness of the substrate-control strategy. Indeed, a limitation inherent in this approach to asymmetric induction is that in most cases direct access to only one diastereoisomer is feasible. What does one do if a chiral substrate molecule enforces the formation of the unwanted diastereoisomer? Faced with this dilemma, a synthetic chemist using a substrate-control strategy would have to redesign the synthetic pathway, selecting a different starting material and/or synthetic intermediates. Although challenges of this sort can seem irresistible to the intellect, they can also breed circuitous synthetic pathways. For example, let us assume that *exo*-alcohol **11** is the desired product. The one-step production of **11** through a carbonyl addition reaction with achiral CH_3MgX is obviously not a viable option because the inherent diastereofacial preference of norcamphor (**9**) guides the formation of the *endo*-alcohol **10**. Nevertheless, *exo*-alcohol **11** could, in principle, be produced by the three-step reaction sequence presented in Scheme 1 (see dotted arrows). Even though the conversion of norcamphor (**9**) to *exo*-alcohol **11** could be dealt with in this manner, this solution, and others like it, are necessarily indirect.

The 1980s witnessed the emergence of a new strategy capable of addressing the challenges outlined above. This new strategy, the *reagent-control* strategy, employs powerful enantiomerically pure catalysts and auxiliaries for the purpose of constructing chiral molecules in a diastereo- and enantioselective fashion. The development of the reagent-control strategy has been the subject of some excellent discussions and reviews.^{5,6} The Sharpless asymmetric epoxidation (SAE) reaction, discovered in 1980,^{7,8} is exemplary of this new strategy for the achievement of stereochemical control. Using titanium(IV) tetrakisopropoxide, *tert*-butyl hydroperoxide, and an enantiomerically pure dialkyl tartrate, the SAE reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity. This powerful reaction is very predictable (see Figure 1). When the (–)-tartrate ligand is used in the SAE reaction, the oxygen atom is delivered to the top face of the olefin when the allylic alcohol is depicted as in Figure 1 (i.e. OH group in lower right-hand corner). The (+)-tartrate ligand, on the other hand, allows the bottom face of the olefin to be epoxidized. When achiral allylic alcohols are employed, the SAE reaction exhibits exceptional enantiofacial selectivity (ca. 100:1), and provides convenient access to synthetically versatile epoxy alcohols.^{8a,9,10} The procedure originally disclosed by Katsuki and Sharpless in 1980 has been modified. Although we will not discuss these modifications here, it is important to note that the SAE reaction can be conducted very successfully with a catalytic amount of the titanium–tartrate complex, provided that molecular sieves are added to the reaction medium.

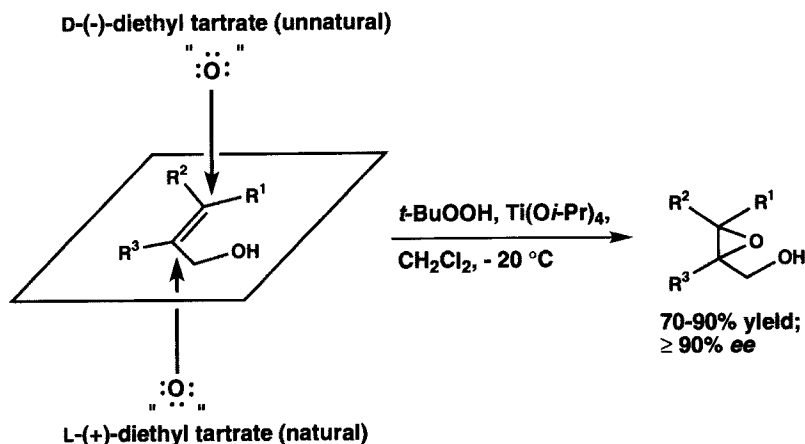
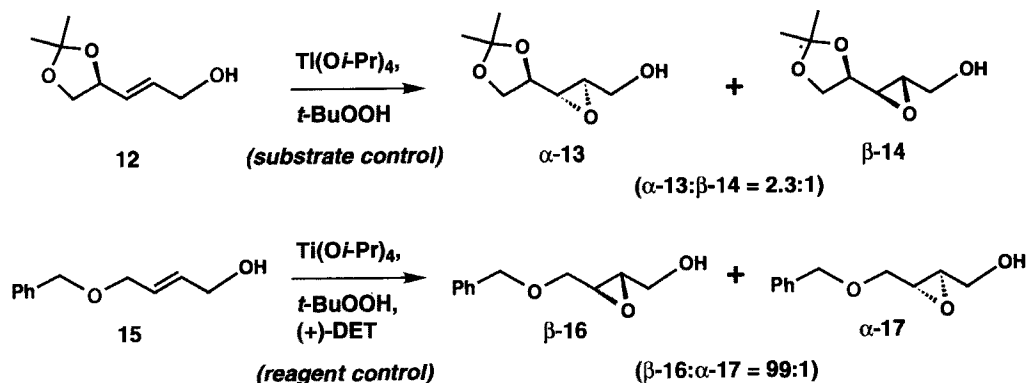


Figure 1. Stereofacial selectivity rule for the Sharpless asymmetric epoxidation.

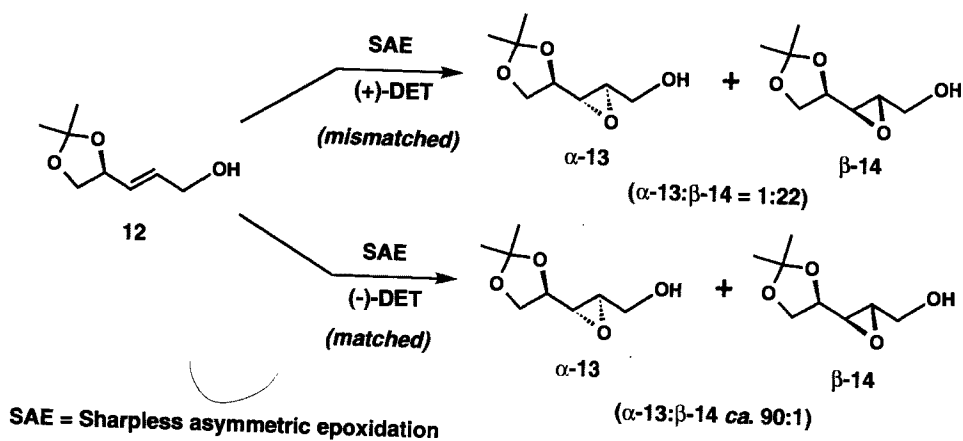
In light of the previous discussions, it would be instructive to compare the behavior of enantiomerically pure allylic alcohol **12** in epoxidation reactions without and with the asymmetric titanium-tartrate catalyst (see Scheme 2). When **12** is exposed to the combined action of titanium tetrakisopropoxide and *tert*-butyl hydroperoxide in the absence of the enantiomerically pure tartrate ligand, a 2.3:1 mixture of α - and β -epoxy alcohol diastereoisomers is produced in favor of α -**13**. This ratio reflects the inherent diastereofacial preference of **12** (substrate-control) for α -attack. In a different experiment, it was found that SAE of achiral allylic alcohol **15** with the (+)-diethyl tartrate [(+)-DET] ligand produces a 99:1 mixture of β - and α -epoxy alcohol enantiomers in favor of β -**16** (98% ee).



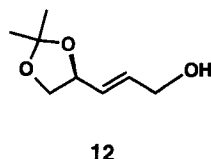
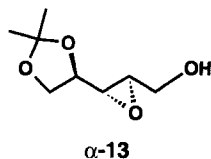
Scheme 2. Substrate-controlled epoxidation of **12** and reagent-controlled epoxidation of **15**.

This result reveals the capacity of (+)-DET to direct an allylic epoxidation (reagent control). But what will happen if we mix enantiomerically pure **12** with enantiomerically pure (+)-DET in an SAE reaction (Scheme 3)? You will recall that the stereocenter in **12** directs the formation of the α -epoxide **13** to the extent of 2.3:1, whereas the chiral reagent (+)-DET enforces an epoxidation of the β -face with a selectivity of 99:1. In this interesting double asymmetric induction experiment^{5,6} the chiral reagent (+)-DET wins out and β -epoxy alcohol **14** is preferentially produced in a 22:1 ratio with the diastereoisomeric α -epoxide **13**. The pairing of substrate **12** with (+)-DET constitutes a *mismatched*⁶ case because the two components have opposite stereofacial preferences. This instructive example highlights the following virtue of the reagent-control strategy: *through the application of powerful enantiomerically pure reagents or catalysts, it is often possible to overwhelm the modest diastereofacial preferences exhibited by a chiral substrate molecule.*⁵

The example also underscores the important fact that only the most powerful reagents or catalysts will be successful in the reagent-control strategy. For example, let us assume that (+)-DET exhibits a β : α preference of 95:5 instead of 99:1, and that the asymmetric substrate **12** has a preference of 5:1 to 10:1 in the opposite direction. If these two components are pitted against each other in the crucial mismatched pairing, then the desired diastereoisomer β -**14** would be formed with a selectivity of less than 4:1. By contrast, the mismatched combination of a highly selective reagent (99:1) with the same moderately selective substrate (5:1 to 10:1 preference) would afford the desired product with useful margins of selectivity (i.e. > ca. 10:1). Incidentally, when allylic alcohol **12**



Scheme 3. Asymmetric epoxidation of allylic alcohol **12**: double asymmetric induction.



(2.3:1 α -selectivity) is subjected to SAE with (–)-DET (high α -selectivity) as the chiral reagent, α -epoxy alcohol α -13 is produced with excellent selectivity (ca. 90:1) (Scheme 3). The pairing of substrate 12 with (–)-DET constitutes a *matched*⁶ case because the two components have the same stereofacial preference; the diastereofacial preference of the titanium–tartrate complex derived from $\text{Ti}(\text{O}i\text{-Pr})_4$ and (–)-DET is reinforced by the chiral substrate's own intrinsic diastereofacial preference. Very good diastereoselectivity is expected in this case.

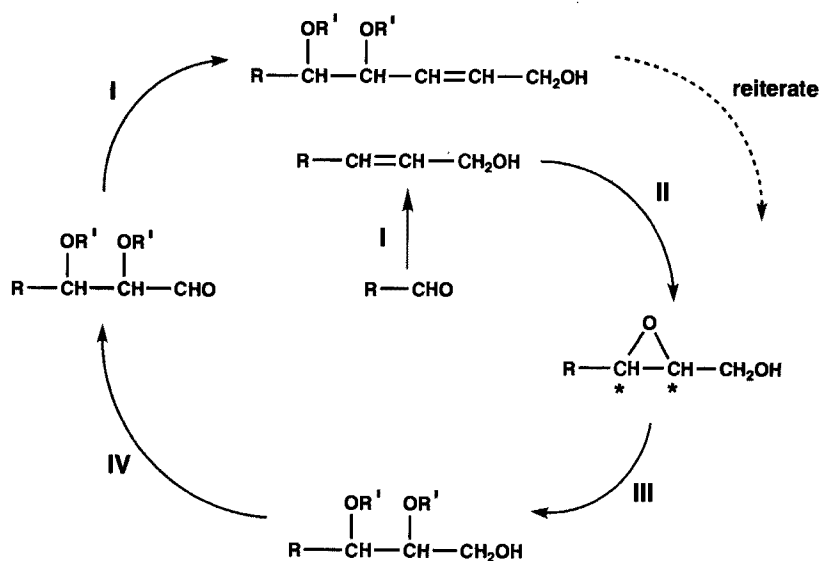
The results summarized in Scheme 3 illustrate that the Sharpless asymmetric epoxidation reaction does indeed satisfy the stringent demand placed upon it by the reagent-control strategy; because the chiral titanium–tartrate complex exhibits a much larger diastereofacial preference than the asymmetric substrate, the influence of the former dominates. As a result, the titanium–tartrate reagent will exert substantial control in both mismatched and matched cases. “In summary, diastereoselectivity, not enantioselectivity, is the crucial issue here. Many reagents are enantioselective, but only a few such reagents are powerful enough to be also diastereoselective in both the matched and mismatched sense.”⁵

The examples addressed thus far adequately convey the utility of the SAE reaction as a tool for the reagent-control strategy. Nonetheless, the power of the SAE reaction and the capabilities of the new reagent-control strategy are demonstrated even more forcefully in the total synthesis of all eight L-hexoses (compounds 1–8) by the groups of Masamune and Sharpless.¹¹ The remainder of this chapter is devoted to this elegant joint venture.

19.2 Retrosynthetic Analysis and Strategy

The hexoses support a concatenation of four contiguous hydroxyl-bearing stereocenters. By virtue of the fact that each stereoisomeric form (16 stereoisomers in all) is known, the hexoses were considered to be ideal targets to demonstrate the utility of the new reagent-control strategy. To cope with the wealth of oxygenation that characterizes the hexoses, it was deemed prudent to employ a synthetic strategy featuring the powerful SAE reaction. It was, however, recognized that a strategy based on the iterative application of the SAE reaction would require the development and employment of methodology that would allow the intermediate 2,3-epoxy alcohols to be manipulated in a regio- and stereocontrolled fashion.

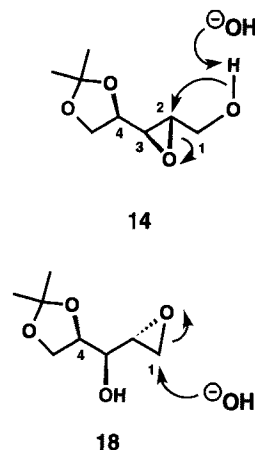
The essential features of the Masamune–Sharpless hexose synthesis strategy are outlined in a general way in Scheme 4. The strategy is based on the reiterative application of a two-carbon extension cycle. One cycle comprises the following four key transformations: (I) homologation of an aldehyde to an allylic alcohol; (II) Sharpless asymmetric epoxidation of the allylic alcohol;

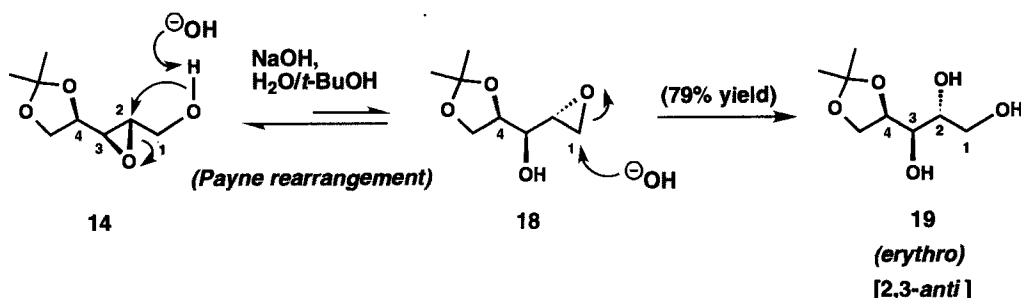


Scheme 4. The Masamune–Sharpless reiterative two-carbon extension cycle.

(III) stereospecific and regioselective opening of the oxirane ring; and (IV) oxidation of the primary alcohol to the corresponding aldehyde, thereby setting the stage for another cycle. This concise and flexible strategy thus provides several opportunities for controlling stereochemical relationships. With respect to stage I of the cycle, it ought to be possible to define the geometry of the allylic alcohol via an *E*- or *Z*-selective Wittig reaction.¹² In stage II, the stereo-directing influence of the appropriate tartrate ligand determines which enantioface of the allylic alcohol is epoxidized. But even if the first two stages proceed with exceptional stereoselectivity – and there is good reason to believe that they will – correct relative stereochemical relationships can be secured only in the event that the intermediate epoxy alcohol can be manipulated in a regio- and stereoselective manner (stage III).

It is appropriate at this juncture to address some of the more useful transformations of 2,3-epoxy alcohols.^{9,13} A 2,3-epoxy alcohol such as compound **14** possesses two obvious electrophilic sites: one at C-2, and the other at C-3. But in addition, C-1 of a 2,3-epoxy alcohol also has latent electrophilic reactivity. For example, exposure of **14** to aqueous sodium hydroxide solution results in the formation of triol **19** in 79% yield (see Scheme 5). In this interesting transformation, hydroxide ion induces the establishment of an equilibrium between 2,3-epoxy-1-ol **14** and the isomeric 1,2-epoxy-3-ol **18**. This reversible, base-induced epoxide migration reaction is a process known as the Payne rearrangement.¹⁴



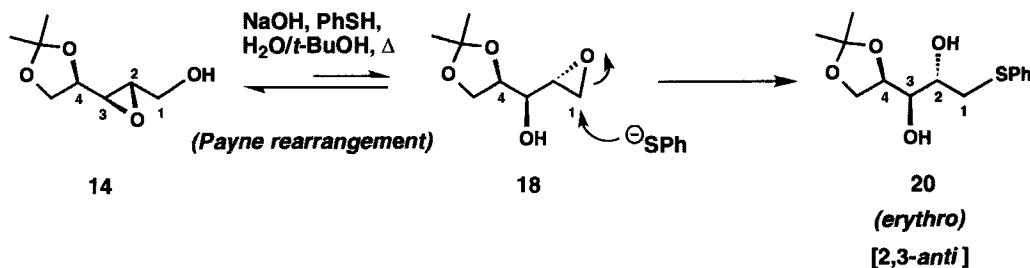


Scheme 5. Payne rearrangement/epoxide opening reaction: hydroxide nucleophile.

Although compound **14** may be preferred at equilibrium, C-1 in isomer **18** is particularly susceptible to nucleophilic attack because it is much less hindered than either C-2 or C-3 in **14**. Once **18** is produced, it reacts selectively with hydroxide ion to give triol **19**. The irreversible conversion of **18** to triol **19** drives the equilibrium process forward.

At first glance, the Payne rearrangement/epoxide opening reaction presented in Scheme 5 would appear to be ideally suited for the production of polyhydroxylated materials such as the hexoses. However, triol **19** contains three free hydroxyl groups and would most certainly be difficult to manipulate selectively; indeed, the employment of an intermediate such as triol **19** in the reiterative cycle (Scheme 4) would necessitate the execution of awkward protection-deprotection steps. Another drawback of the triol route is that the regioselectivity for attack at C-1 by hydroxide ion is not always acceptable. You will note that opening of the epoxide ring through attack at C-2 in **18** and/or C-3 in **14** would afford two different diastereoisomers of **19**.

The discovery by the groups of Masamune and Sharpless that the addition of a suitable nucleophile to the equilibrating mixture of epoxy alcohols can result in the selective interception of the less hindered 1,2-epoxy-3-ol isomer (i. e. **18**) has significantly extended the synthetic utility of the Payne rearrangement.^{9,13} For example, addition of thiophenol to an equilibrating mixture of compounds **14** and **18** in refluxing aqueous sodium hydroxide/*tert*-butanol results



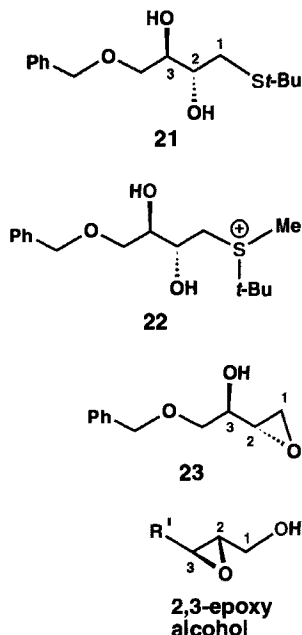
Scheme 6. Payne rearrangement/epoxide opening reaction: thiolate nucleophile.

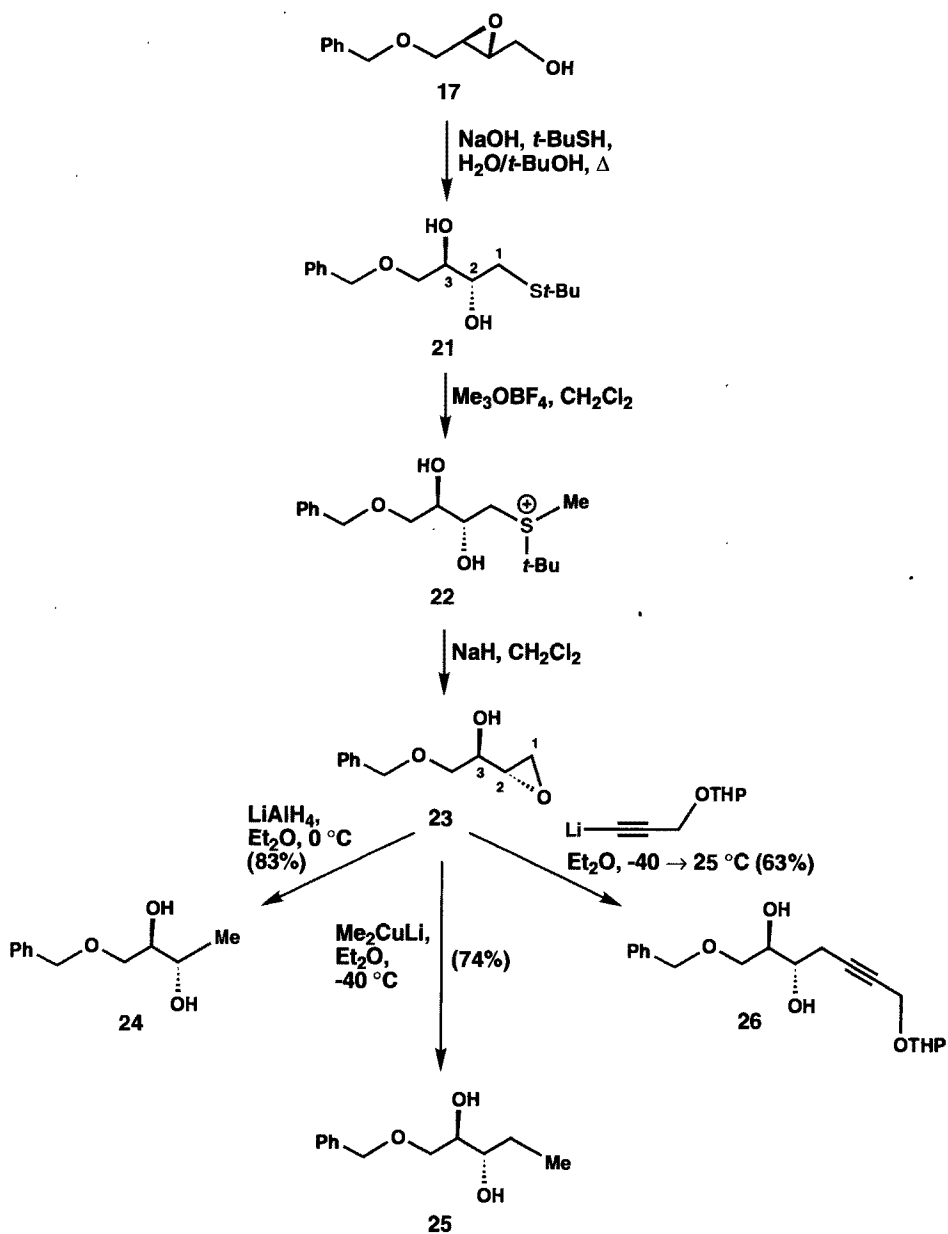
in the formation of 1-phenylthio-2,3-diol **20** (see Scheme 6). In this reaction, once 1,2-epoxy-3-ol **18** is produced via a Payne rearrangement, it is regioselectively and irreversibly captured by the thiolate nucleophile to give **20**. The net conversion of **14** to **20** can thus be smoothly accomplished because compound **18** is continuously regenerated via Payne rearrangement of **14**. It is important to note that the regioselectivity exhibited for attack at C-1 by the thiolate nucleophile is usually very good, provided that the epoxy alcohol substrate possesses an oxygen substituent at C-4.^{13d,e} In the case of epoxy alcohol **14**, branching (steric hindrance) at C-4 and the electron-withdrawing inductive effect of the C-4 acetonide oxygen discourage nucleophilic attack at the adjacent C-3 position.

For the Payne rearrangement/epoxide opening reaction to be successful, the nucleophile must obviously be compatible with an alkaline aqueous medium. Although this prerequisite significantly reduces the number of potential nucleophiles, Sharpless *et al.* found that 1-alkylthio-2,3-diols (e.g. see **21**, Scheme 7) can be converted to isolable 1,2-epoxy-3-ols (see **23**) via a two-step sequence that includes selective alkylation of the sulfur atom with Meerwein's salt (Me_3OBF_4) (see **21** \rightarrow **22**), followed by base-induced ring closure (see **22** \rightarrow **23**).^{9a,13d} Isolable 1,2-epoxy-3-ols such as **23** can subsequently be employed in regioselective epoxide ring opening reactions with a variety of nucleophiles in an organic solvent (for examples, see **23** \rightarrow **24**; **25**; **26**, Scheme 7). It is noteworthy that the latter three transformations can be conducted without prior protection of the free hydroxyl group in **23**.

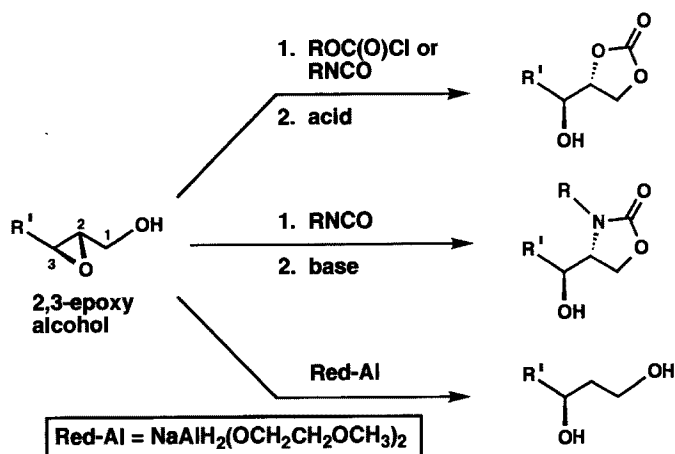
Some of the more popular transformations of 2,3-epoxy alcohols in organic synthesis are presented in Scheme 8. In each transformation,⁹ a function with nucleophilic properties is affixed to the free C-1 hydroxyl group. In this manner, the C-1 oxygen atom can direct the regiochemical course of the subsequent epoxide ring opening reaction. The reaction types presented in Scheme 8 are, in fact, highly regioselective, affording products from intramolecular nucleophilic attack at C-2.

With respect to the total synthesis of the hexoses, the transformation presented in Scheme 6 is particularly promising. In contrast to the three free hydroxyl groups in intermediate **19** (see Scheme 5), compound **20** has only two free hydroxyl groups. Moreover, the sulfur substituent in **20** can be regarded as a latent carbonyl group. After protection (i.e. acetonation) of the vicinal hydroxyl groups in **20**, oxidation of the sulfur atom to the corresponding sulfoxide, followed by the execution of a Pummerer rearrangement¹⁵ could provide ready access to the targeted C-1 aldehyde. Of course, if successful, this reaction sequence would obviate the need for tedious protecting group manipulations. It is important to emphasize that a Pummerer rearrangement would constitute a mild and effective method for the establishment of the requisite aldehyde oxidation level at C-1. In contrast to conventional alcohol oxidation protocols, a Pummerer rearrangement is less likely to lead to epimerization of the α C-2 stereocenter.





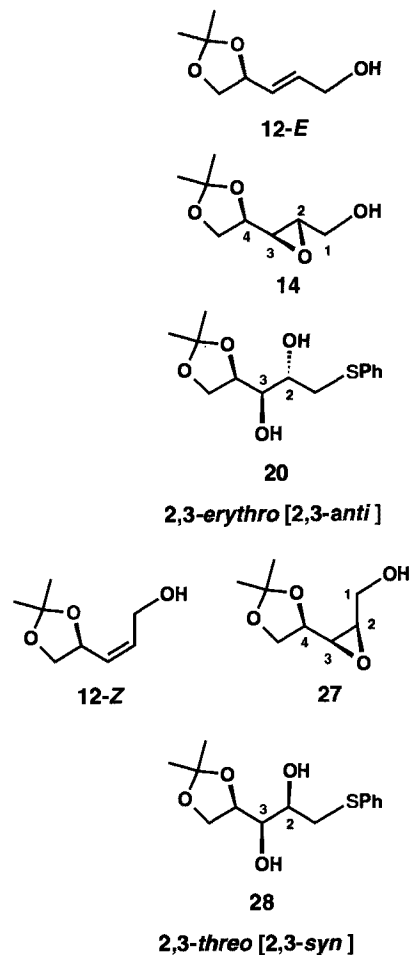
Scheme 7. Synthesis and selected transformations of 1,2-epoxy-3-ol **23**.

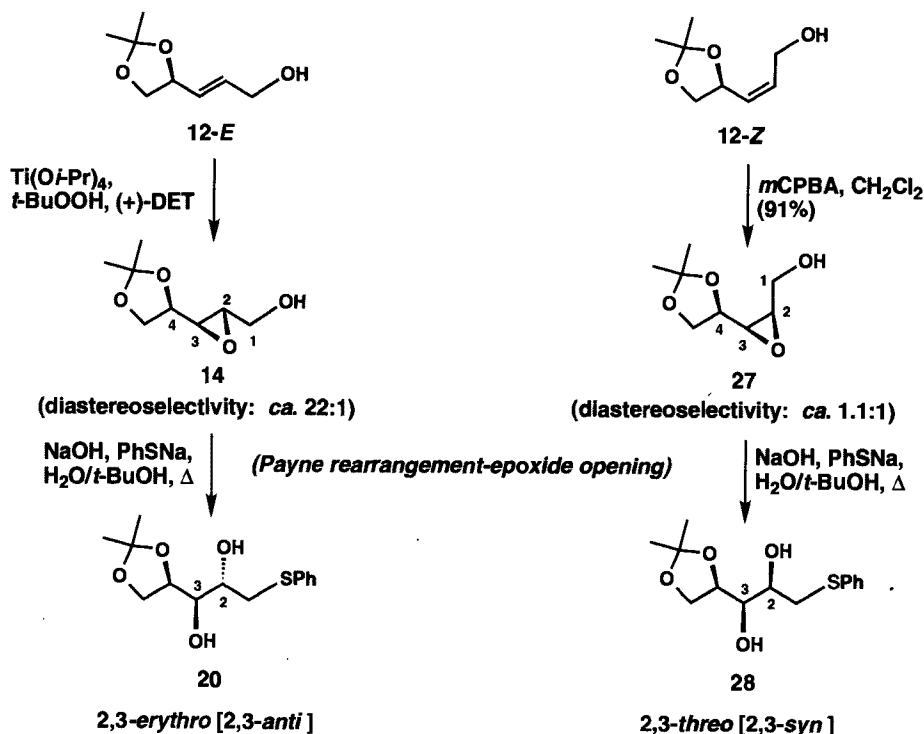


Scheme 8. Selected transformations of 2,3-epoxy alcohols.

During the course of the Masamune–Sharpless hexose project, an important problem arose. As we have already seen, asymmetric epoxidation of enantiomerically pure *trans* allylic alcohol **12-E** (see Scheme 9) with (+)-DET affords 2,3-epoxy alcohol **14** with 22:1 diastereoselectivity. When **14** is subsequently subjected to the action of sodium benzenethiolate under Payne rearrangement conditions, *erythro* 2,3-diol **20** is produced stereospecifically and with high regioselectivity. The stereoisomeric *cis* allylic alcohol **12-Z**, on the other hand, is not a viable substrate for SAE with (–)-DET. *Z* Allylic alcohols bearing a stereocenter in proximity to the olefin are, in fact, notoriously poor substrates for SAE, reacting slowly and often with low stereoselectivity. Compound **12-Z** can, however, be epoxidized with *meta*-chloroperbenzoic acid (*m*CPBA) to give a mixture of epoxy alcohol **27** and its diastereoisomer in excellent chemical yield (91%), but with essentially no diastereoselectivity. Thus, even if compound **27** could be isolated in pure form and subsequently converted to *threo* 2,3-diol **28** via the Payne rearrangement/opening process, the inability to oxidize **12-Z** in a stereoselective fashion undermines the viability of this pathway to the requisite *threo* diastereomer **28**. This problem is particularly serious because the development of a unified strategy for the synthesis of the hexoses requires the discovery of an effective solution to the *threo* 2,3-diol problem.

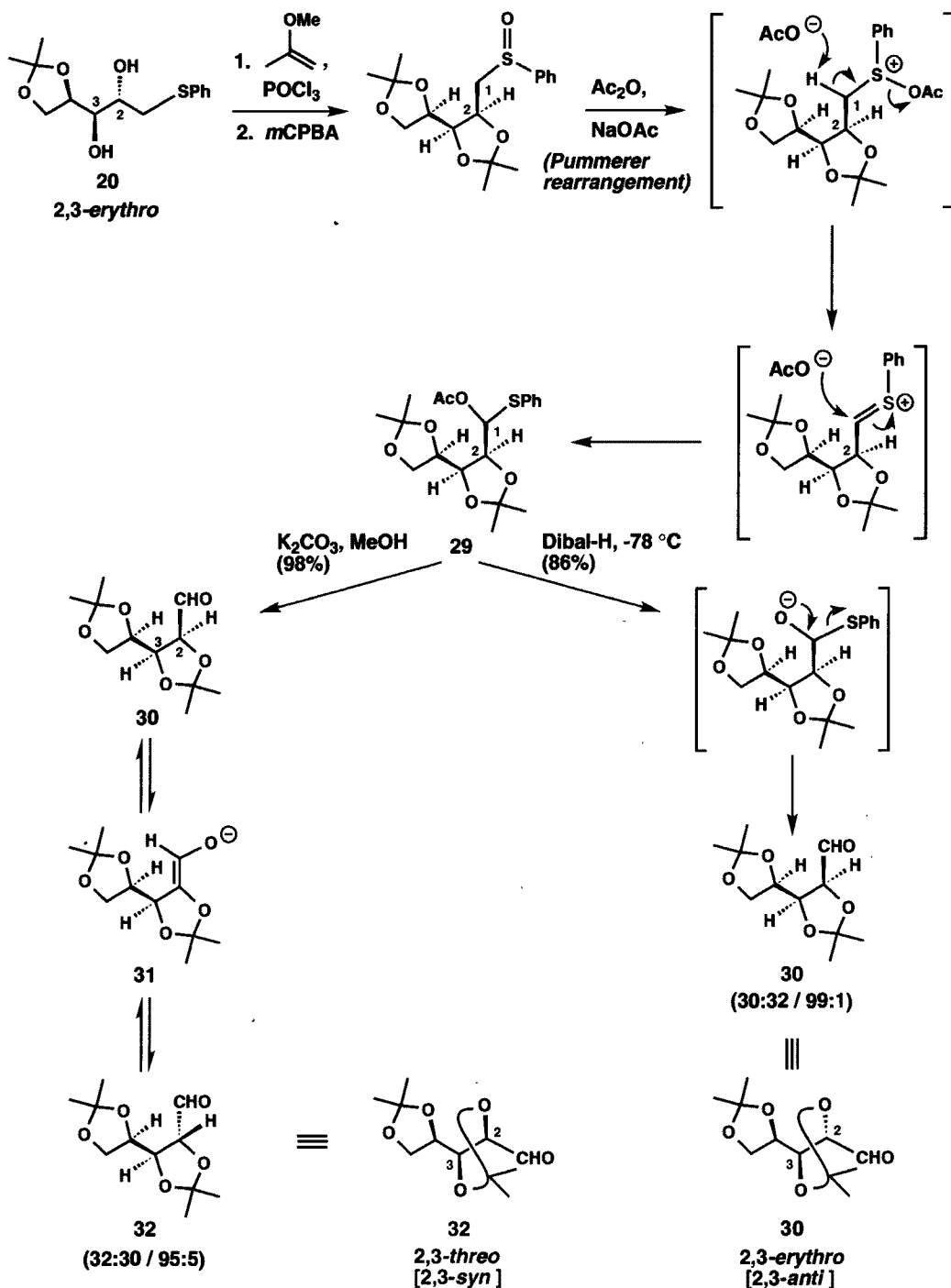
A careful analysis of this problem led to the identification of an exceedingly simple solution (see Scheme 10). The Masamune–Sharpless solution to the *threo* 2,3-diol problem actually takes advantage of the ready availability of the *erythro* 2,3-diol diastereoisomer. As we have seen in Scheme 9, *erythro* 2,3-diols such as **20** can be conveniently assembled from *trans* allylic alcohols via sequential SAE and Payne rearrangement/epoxide opening reac-





Scheme 9. The *threo* 2,3-diol problem. The *erythro/threo* notation is based on Fischer projection formulas. For example, if *threo* 2,3-diol **28**, shown here in a staggered zigzag conformation, was depicted in an eclipsed Fischer projection, the adjacent hydroxyls attached to carbons 2 and 3 would reside on opposite sides of the carbon chain. An alternative, perhaps less ambiguous, descriptor is the *syn/anti* notation.^{6a}

tions. After simultaneous protection of the vicinal hydroxyl groups in *erythro* **20** in the form of a cyclic ketal, oxidation of the sulfur atom to the corresponding sulfoxide with $m\text{CPBA}$, followed by Pummerer rearrangement,¹⁵ affords geminal acetoxy sulfide **29** (Scheme 10). The acetoxythioacetal function in **29** is simply a latent aldehyde carbonyl, and it was anticipated that the conversion of the former function to the latter could be brought about with potassium carbonate in methanol. But in addition to this desired and expected change, it was hoped that mutual steric repulsion between the newly formed C-1 aldehyde and the C-3 substituent in *erythro* **30** would provide the impetus for a base-induced epimerization at C-2 to give the more stable (less congested) *trans* or *threo* diastereoisomer **32**. Gratifyingly, exposure of **29** to the action of basic methanol accomplishes both the solvolytic cleavage of the acetoxythioacetal function and the desired epimerization at C-2 to give a 95:5 mixture of compounds **32** and **30** in favor of *threo* aldehyde **32** (ca. 98% total yield). The C2–C3 cyclic ketal (isopro-



Scheme 10. Acetoxythioacetal cleavage with and without epimerization at C-2.

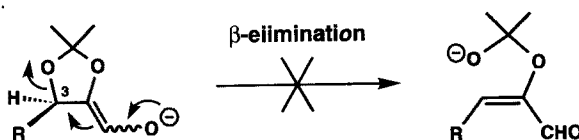
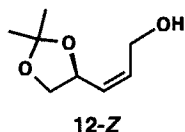
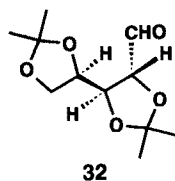
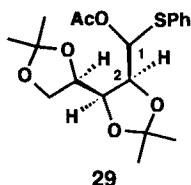
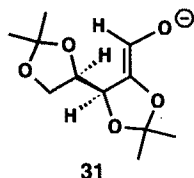
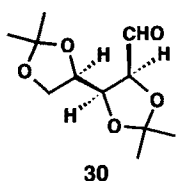


Figure 2. Orthogonality between the enolate π system and the C3–O σ bond prevents a destructive β -elimination.

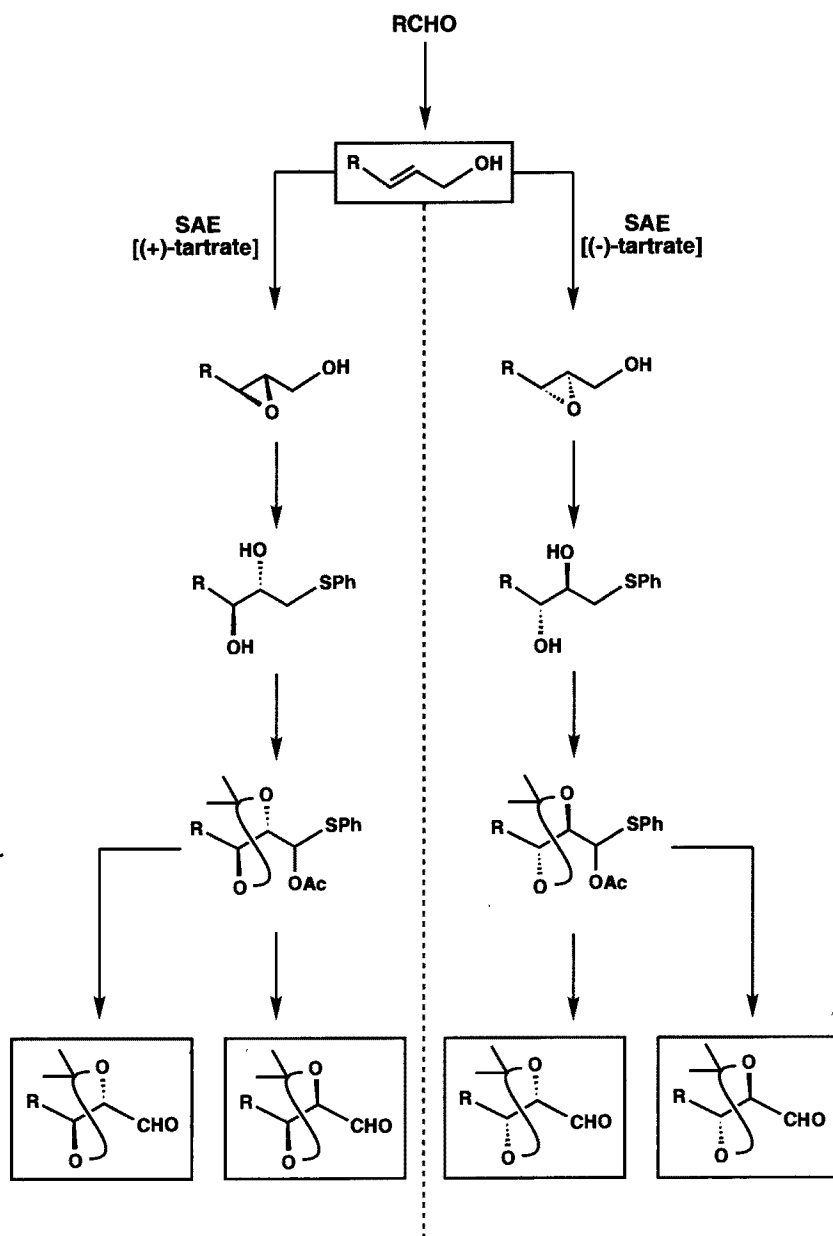


pylidene ketal) thus serves several important functions in the reaction sequence presented in Scheme 10; in addition to its obvious role as a protecting group, the C2–C3 cyclic ketal in compound **30** creates an ideal setting for the desired epimerization at C-2.

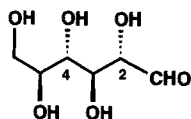
At first glance, it may seem surprising that enolate **31**, produced on deprotonation of the α carbon (C-2) in **30**, does not initiate a β -elimination of the C-3 alkoxy substituent. After all, enolates containing alkoxy groups or other heteroatom functions in the β position are, in many instances, prone to a destructive β -elimination pathway. In the context of **31**, however, the C2–C3 cyclic ketal prevents a destructive β -elimination by maintaining orthogonality between the enolate π system and the C3–O σ bond (see Figure 2).^{13c,16} To summarize, the *threo* 2,3-diol problem is solved simply by conducting the cleavage of the acetoxythioacetal function in a sufficiently basic medium, so that epimerization at C-2 can also take place.

But how susceptible is *erythro* aldehyde **30** to epimerization at C-2? Can the conversion of acetoxythioacetal **29** to *erythro* aldehyde **30** be accomplished in a manner that does not compromise the integrity of the stereocenter at C-2? These two questions are critical because the acquisition of both *threo* and *erythro* diastereomeric forms is a necessary precondition for the total synthesis of the eight L-hexoses (**1**–**8**). On the basis of the observations presented in Scheme 10, it is clear that a basic reagent in a hydroxylic solvent can induce facile epimerization at C-2 in **30** to give a mixture enriched in the diastereoisomeric *threo* aldehyde **32**. Thus, the conversion of **29** to **30** would have to be brought about by using a reagent that is not basic. In the event that a reductive cleavage of the C-1 acetoxy grouping in **29** could be achieved, then the desired aldehyde **30** would be revealed simply upon collapse of the tetrahedral alkoxide intermediate with concomitant expulsion of benzenethiolate anion. Gratifyingly, exposure of acetoxythioacetal **29** to the action of diisobutylaluminum hydride (Dibal-H) brings about the desired cleavage, affording *erythro* aldehyde **30** in 86% yield; essentially no epimerization at C-2 occurs under these conditions.

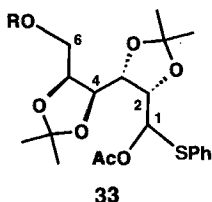
The simple and elegant tactic of cleaving the acetoxythioacetal function in **29** either with or without concomitant epimerization at C-2 effectively avoids the problematic (nonstereoselective) epoxidation of chiral Z allylic alcohols such as **12-Z** (see Scheme 9).



Scheme 11. General strategy for the achievement of stereochemical control in the synthesis of the hexoses 1-8.



1: L-allose

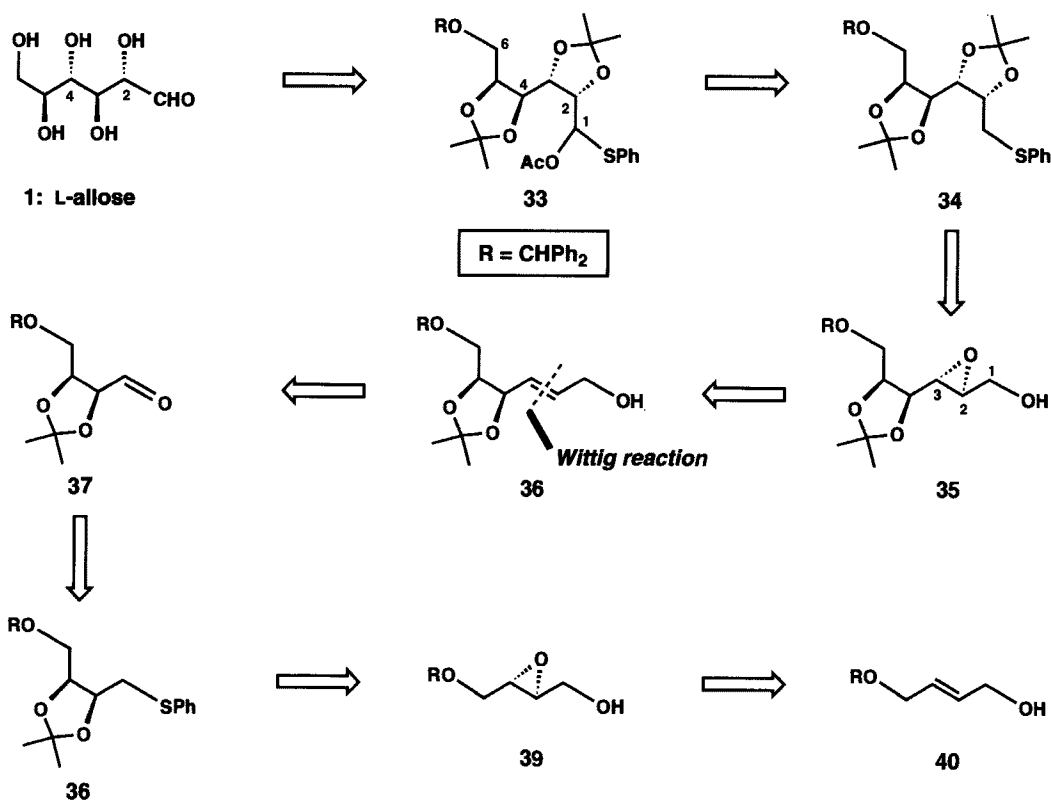


The general strategy presented in Scheme 11 could, therefore, permit the construction of any given saccharide stereoisomer from a common *trans* allylic alcohol. It was anticipated that the SAE reaction with either (+)- or (–)-DET, and the acetoxythioacetal cleavage step with either basic methanol or Dibal-H would allow the configurations of the newly formed hydroxyl-bearing stereocenters to be established with full control. It is important to note that the aldehyde stereoisomers to the left and to the right of the dotted line in Scheme 11 have a true mirror image relationship when group R is achiral. In subsequent turns through the cycle (Scheme 4), however, group R is chiral and each pair of aldehydes to the left and to the right of the dotted line are diastereomeric. As a result, the success of a reaction to the right of the dotted line does not guarantee the success of the corresponding reaction to the left of the line or *vice versa*.

The Masamune–Sharpless synthesis of L-allose (**1**) is outlined retrosynthetically in Scheme 12. Through a straightforward sequence of deprotections, L-allose (**1**) could be derived from compound **33**. An important step in the conversion of **33** to **1** is the cleavage of the C-1 acetoxythioacetal function. As we have already witnessed in Scheme 10, there are at least two different ways in which the cleavage of an acetoxythioacetal function can be brought about. These two methods are, in fact, complementary. In this particular case, the absolute configuration at C-2 in **33** is the same as the configuration at C-2 in L-allose (**1**): both are *S*. Therefore, the cleavage of the C-1 acetoxythioacetal function in **33** must be accomplished without compromising the adjacent stereocenter at C-2. On the basis of Scheme 10, the action of Dibal-H on **33** should induce the desired cleavage without disturbing the C-2 stereocenter.

With the aldehyde oxidation state at C-1, compound **33** could, in the synthetic direction, be fashioned through a Pummerer rearrangement of the sulfoxide derived from sulfide **34**. The latter compound could, in turn, be derived in two steps from epoxy alcohol **35**. Although **35** has electrophilic potential at carbons 1, 2, and 3, benzenethiolate anion will react selectively with C-1 in a strongly basic medium. As shown in Scheme 6, the action of hydroxide ion on a 2,3-epoxy-1-ol such as **35** would result in the establishment of a Payne rearrangement equilibrium with the isomeric 1,2-epoxy-3-ol. The oxirane ring of the latter substance can then be opened in a regioselective fashion through attack at C-1 by the thiolate nucleophile. Simultaneous protection of the vicinal hydroxyl groups in the form of an isopropylidene ketal (cyclic ketal) would then complete the synthesis of **34**.

From a stereochemical point of view, compound **35** is rather complex, for it possesses four contiguous oxygen-bearing stereocenters. Nonetheless, compound **35** is amenable to a very productive retrosynthetic maneuver. Indeed, removal of the epoxide oxygen from **35** furnishes *trans* allylic alcohol **36** as a potential precursor. In the synthetic direction, SAE of **36** with the (+)-dialkyl tartrate ligand would be expected to afford epoxy alcohol **35**, thus introducing two of the four contiguous stereocenters in one step.

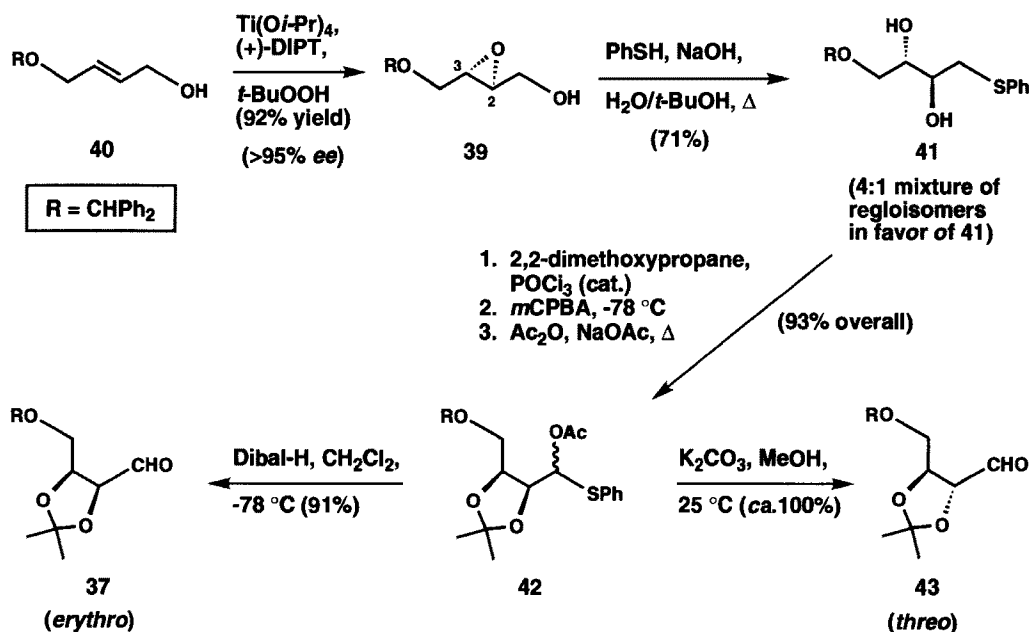


Scheme 12. Retrosynthetic analysis of L-allose (1).

Retrosynthetic cleavage of the carbon–carbon double bond in **36** provides aldehyde **37** as a potential precursor. At this stage of the synthesis, the venerable Wittig reaction¹² could be relied upon to establish the requisite *trans* double bond geometry in **36**. Through sequential oxidation, Pummerer rearrangement, and acetoxythioacetal cleavage reactions, aldehyde **37** could be fashioned from sulfide **38**, the projected product of a Payne rearrangement/epoxide opening reaction of epoxy alcohol **39**, followed by acetonation. Finally, epoxy alcohol **39** could be derived in one step from *trans* allylic alcohol **40**. The latter compound, a simple, prochiral four-carbon building block, could serve as the common starting material for all sixteen hexoses (L and D). Although a retrosynthetic analysis for only one of the hexoses is illustrated, it is important to note that all of the hexose stereoisomers could, in principle, be assembled in short order from compound **40** via pathways employing the same fundamental reaction processes.

19.3 Total Synthesis

The Masamune–Sharpless synthesis of the L-hexoses commences with the asymmetric epoxidation of 4-benzhydryloxy-(*E*)-but-2-en-1-ol (**40**) with (+)-diisopropyl tartrate [(+)-DIPT] as the chiral ligand (see **40** → **39**, Scheme 13). Incidentally, compound **40** can be conveniently prepared from commercially available (*Z*)-2-buten-1,4-diol through sequential monoprotection, PCC oxidation/isomerization, and reduction reactions. Because the synthetic sequence commences with a *trans* allylic alcohol, step I of the reiterative cycle (Scheme 4) is unnecessary. The asymmetric epoxidation of **40** thus constitutes the initial step. It is instructive to note at this stage that the four carbon atoms in **39** correspond to C-3 through C-6 of the hexoses. In particular, the stereogenic center at position 3 in **39** corresponds to the C-5 stereocenter in the L-hexoses. Since the configuration of the C-3 stereocenter in **39** is conserved throughout the synthetic sequence, the sense of chirality of the tartrate ligand dictates the handedness of the carbohydrate products. Therefore, the use of the (+)-tartrate ligand in the initial asymmetric epoxidation step will permit the synthesis of the L-hexoses. Of course, the D-hexoses could be prepared via the same synthetic scheme simply by using the (–)-tartrate ligand in the initial asymmetric epoxidation step. The selection of the appropriate tartrate



Scheme 13. Synthesis of intermediates **37** and **43**.

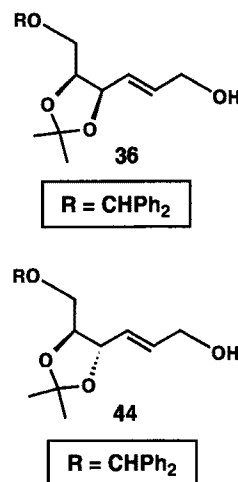
ligand in subsequent asymmetric epoxidations, and the employment of the appropriate acetoxithioacetal cleavage protocol could then secure the requisite diastereomeric relationships.

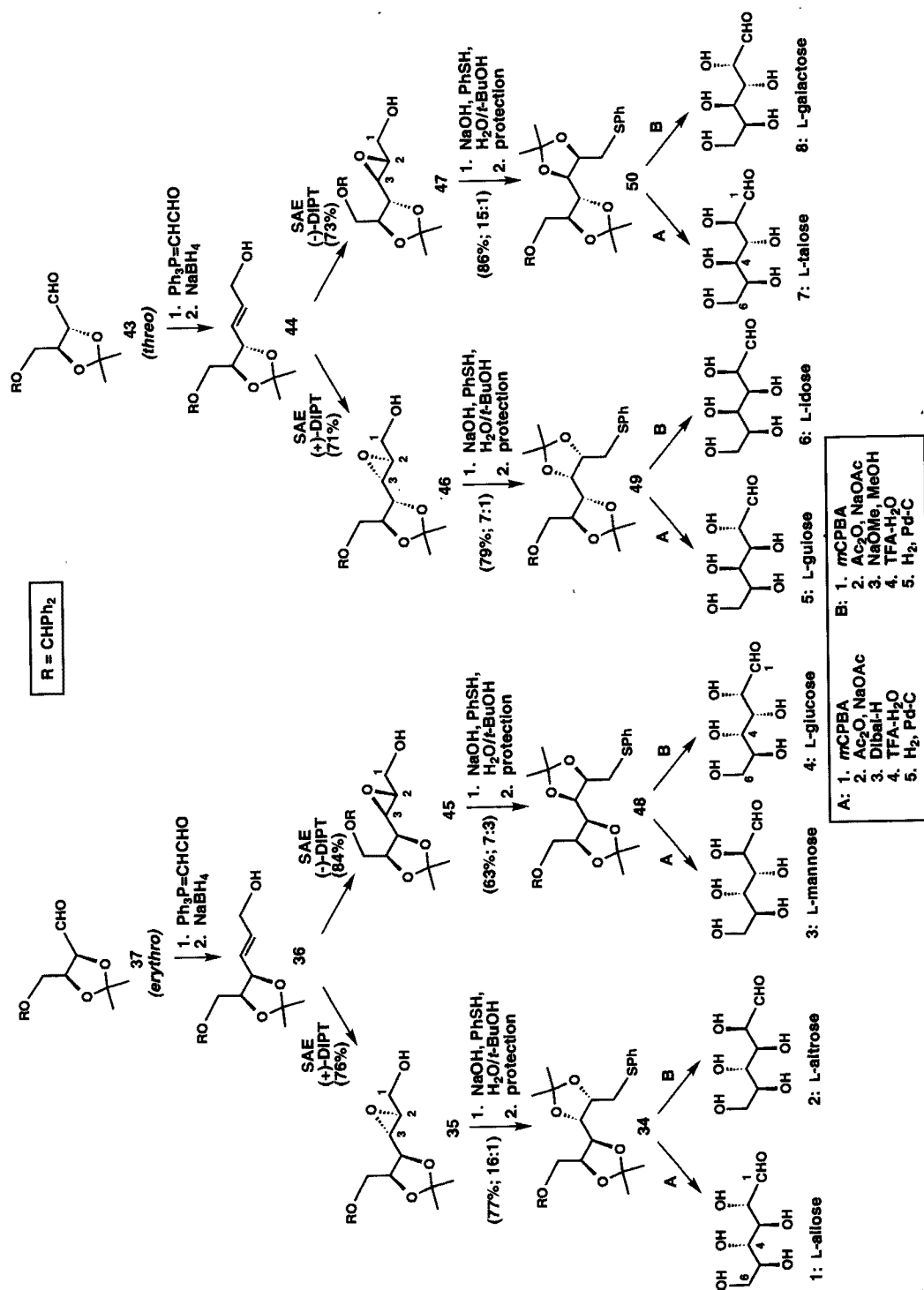
2,3-Epoxy alcohol **39** is produced with >95 % *ee* by SAE of **40**, and is poised for a Payne rearrangement/epoxide opening reaction. In the event, exposure of **39** to thiophenol in a basic medium results in the formation of a 4:1 mixture of regioisomeric diol sulfides in favor of the desired C-1 opened product **41**. Recrystallization of the 4:1 mixture furnishes compound **41** in 71 % yield. As we have seen in Schemes 5 and 6, the action of hydroxide ion on a 2,3-epoxy-1-ol, such as **39**, induces the establishment of a Payne rearrangement equilibrium between **39** and an isomeric 1,2-epoxy-3-ol. The Payne rearrangement process is stereospecific; the initially formed C-1 alkoxide initiates opening of the adjacent oxirane ring by attacking C-2 with inversion of configuration. There is thus a correspondence between the stereochemistries of the starting 2,3-epoxy-1-ol and the isomeric 1,2-epoxy-3-ol that is produced in the Payne rearrangement. Due largely to steric factors, the 1,2-epoxy-3-ol isomer is particularly susceptible to a nucleophilic attack at C-1.

After protection of the contiguous hydroxyls in **41** in the form of a cyclic ketal, sequential oxidation and Pummerer rearrangement reactions furnish acetoxithioacetal **42**. Treatment of **42** with Dibal-H accomplishes the reductive cleavage of the acetoxithioacetal function and affords, virtually without epimerization at C-2, *erythro* aldehyde **37** (91 % yield). If, on the other hand, compound **42** is exposed to K_2CO_3 in methanol, a solvolytic cleavage of the acetoxithioacetal function occurs and the aldehyde thus formed undergoes facile epimerization at C-2 to give *threo* aldehyde **43**, the C-2 epimer of **37** (ca. 100 % yield).

Compounds **37** and **43** are pivotal synthetic intermediates from which all eight of the L-hexose diastereoisomers can be derived (see Scheme 14). The C2–C3 *erythro* stereochemistry of **37** corresponds to the C4–C5 *erythro* stereochemistry of L-allose (**1**), L-altrose (**2**), L-mannose (**3**), and L-glucose (**4**), whereas the C2–C3 *threo* stereochemistry of **43** corresponds to the C4–C5 *threo* stereochemistry of L-gulose (**5**), L-idose (**6**), L-talose (**7**), and L-galactose (**8**). The synthesis of intermediates **37** and **43** marked the completion of the first turn of the cycle and set the stage for the second turn. Independent treatment of compounds **37** and **43** with formylmethylenetriphenylphosphorane smoothly achieves the desired two-carbon extension, furnishing the corresponding *E* α,β -unsaturated aldehydes in excellent yields and with >20:1 stereoselectivity in each case (see Scheme 14). It is noteworthy that epimerization at C-2 does not occur during the course of these Wittig reactions. As expected, sodium borohydride reduction of the two-carbon extended aldehydes, derived respectively from **37** and **43**, proceeds uneventfully and gives the corresponding *E* allylic alcohols, compounds **36** and **44**.

The most crucial stage in the synthesis has been reached. The goal of constructing the L-hexoses from allylic alcohols **36** and **44** can be achieved only in the event that the two diastereotopic olefin

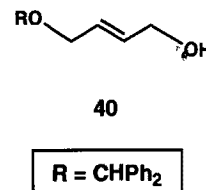




Scheme 14. Syntheses of the L-hexoses (1–8).

faces in each compound can be selectively epoxidized. At the outset, there was little doubt that the asymmetric epoxidation of achiral allylic alcohol **40** would exhibit exceptional stereoselectivity. Allylic alcohols **36** and **44**, on the other hand, are chiral molecules possessing an inherent diastereofacial preference. For the reagent-control strategy to be successful, the stereofacial preference of the asymmetric titanium–tartrate reagent would have to be high enough to enhance (matched case) or override (mismatched case) any pre-existing diastereofacial preference in compounds **36** and **44**. Gratifyingly, the four asymmetric epoxidation reactions extending from *E* allylic alcohols **36** and **44** all exhibit excellent diastereoselectivities (>20:1) (Scheme 14). Subjection of the four diastereomeric epoxy alcohols **35**, **45**, **46**, and **47** to the Payne rearrangement/epoxide opening reaction with benzenethiolate as the nucleophile, followed by protection of the resulting diol sulfides provides compounds **34**, **48**, **49**, and **50**, respectively. Although the regioselectivity exhibited in the Payne rearrangement/epoxide opening of compound **45** is a disappointing 7:3 in favor of the desired regioisomer, the regioselectivities displayed in the other three cases are quite good.

From thioethers **34**, **48**, **49**, and **50**, the synthesis of each of the eight L-hexoses only requires a few steps. As anticipated, sequential sulfur oxidation (*m*CPBA) and Pummerer rearrangement (Ac₂O, NaOAc) reactions smoothly convert the latter four compounds to the corresponding C-1 acetoxythioacetals. With reference to the pathways leading to L-allose (**1**), L-mannose (**3**), L-gulose (**5**), and L-talose (**7**), reductive cleavage of the acetoxythioacetal functions with Dibal-H (no C-2 epimerization), followed sequentially by trifluoroacetic acid (TFA)-induced hydrolysis of the isopropylidene ketals and hydrogenolysis of the benzhydryl protecting groups completes the synthesis of L-hexoses **1**, **3**, **5**, and **7**. On the other hand, solvolytic cleavage of the acetoxythioacetal functions with concomitant epimerization at C-2 using NaOMe in methanol, followed by the execution of straightforward deprotection reactions completes the syntheses of L-altrose (**2**), L-glucose (**4**), L-idose (**6**), and L-galactose (**8**). The total synthesis of the eight L-hexoses via a reagent-control strategy has thus been achieved.



19.4 Conclusion

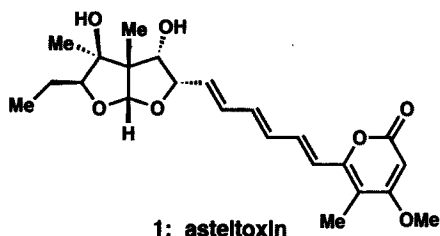
The stereoselective syntheses described in this chapter reveal the power of the reagent-control strategy, demonstrating that the concept of matching and mismatching is valid for the Sharpless asymmetric epoxidation as it is for other important reactions such as the aldol condensation and the Diels–Alder cycloaddition.⁶ The synthetic pathways extending from the monoprotected, achiral four-carbon building block **40** to each of the eight L-hexoses take advan-

tage of the high double asymmetric induction exhibited in the titanium–tartrate catalyzed epoxidation reaction. The simple yet crucial tactic of cleaving an acetoxythioacetal function either with or without C-2 epimerization is also noteworthy. The latter two reaction processes constitute the two elements of stereocontrol that allow the stereoselective and predictable creation of two contiguous oxygen-bearing stereocenters in any desired relative arrangement. Since the mirror-image forms of each of the L-hexoses can be prepared simply by using the enantiomeric tartrate ligand in the initial asymmetric epoxidation step, this elegant work also constitutes a formal synthesis of the D-hexoses.

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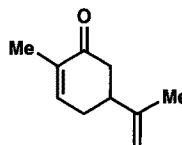
S. L. Schreiber (1983)

Asteltoxin

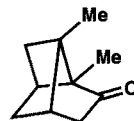
20.1 Introduction

The photo-induced union of two sites of unsaturation to give a four-membered ring is a powerful and general process in organic synthesis. A photochemical [2+2] cycloaddition of two alkenes produces a cyclobutane ring,¹ a strained and valuable substructure that can either be incorporated directly into a natural product or can be employed in subsequent, thermodynamically favored transformations.² The stereochemical potential of [2+2] photocycloadditions of alkenes is evident from the observation that the cyclobutane product can host up to four contiguous asymmetric carbon atoms. Ciamician's discovery, in 1908, that exposure of carvone (I) to Italian sunlight for one year results in the formation of carvonecamphor (II) constitutes the first example of a [2+2] photocycloaddition reaction (see Scheme 1).³ Soon after this important discovery, Ciamician's colleague, Paterno, disclosed the first example of a [2+2] photocycloaddition of an aldehyde to an alkene to give an oxetane⁴ (i. e. a four-membered cyclic ether, see III + IV \rightarrow V, in Scheme 1). Interestingly, these promising transformations went largely unnoticed until G. Büchi and his group at MIT confirmed the four-membered ring containing products for both processes in the 1950's.⁵ Büchi's important studies confirmed the impressive structural transformations that could be achieved in a single step through irradiation of a suitably unsaturated molecule.

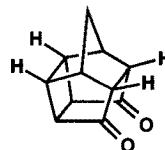
Not surprisingly, light was soon featured in syntheses of numerous complex molecules. In fact, in 1958, only one year after Büchi's confirmation of Ciamician's discovery, Cookson *et al.* reported the facility with which complex cage structures (see VII, Scheme 1) can be constructed through intramolecular [2+2] photo-



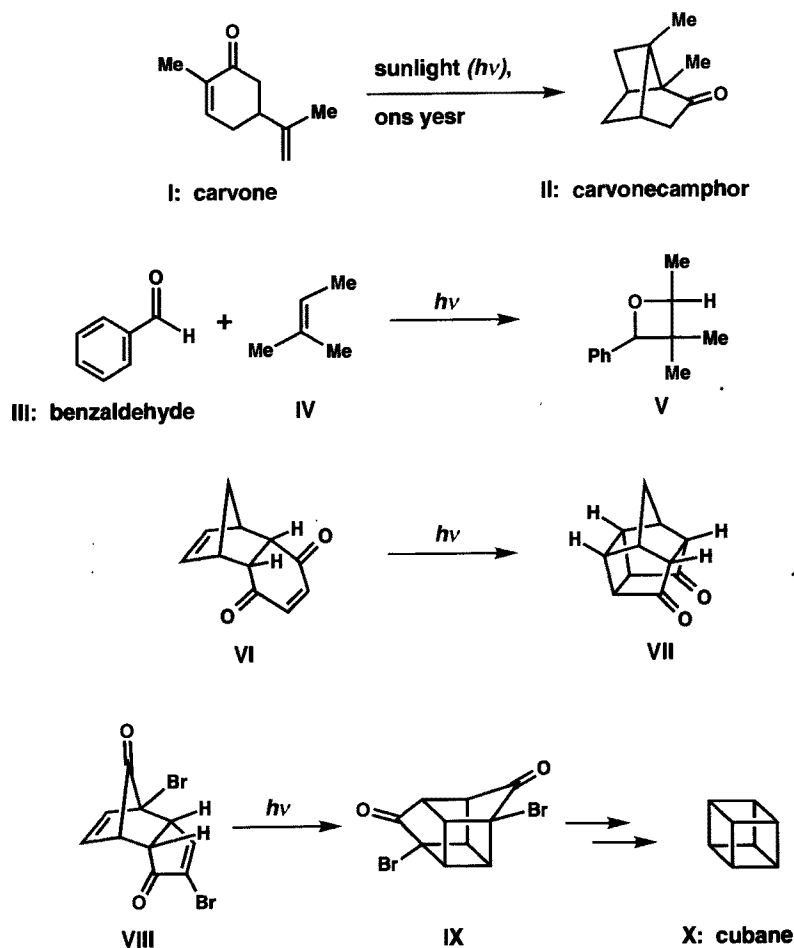
I: carvone



II: carvonecamphor



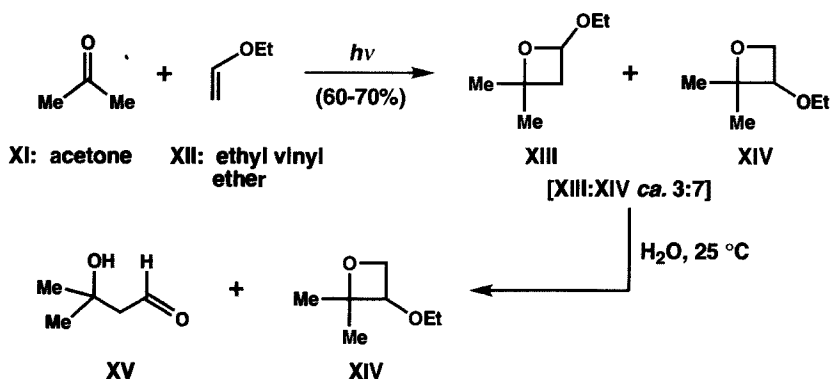
VII



Scheme 1. Representative [2+2] photocycloaddition reactions.

cycloadditions.⁶ Irradiation of VI, the *endo* Diels–Alder adduct derived from cyclopentadiene and *para*-benzoquinone, produces cage structure VII through an internal [2+2] photocycloaddition; two five-membered rings, one four-membered ring, and four new stereogenic centers are created in this elegant and productive process. A key transformation in Eaton's synthesis of the platonic solid, cubane (X), is the intramolecular enone–olefin [2+2] photocycloaddition of intermediate VIII to give compound IX.⁷

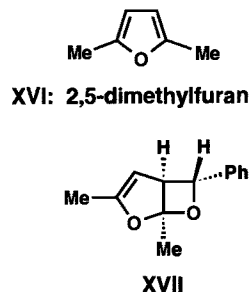
The [2+2] photocycloaddition of an aldehyde or a ketone to an alkene to form an oxetane (e. g. III + IV → V, Scheme 1) is a process that is known as the Paterno–Büchi reaction;⁸ it is a reaction that was first reported by Paterno in 1909⁴ and was confirmed approximately forty-five years later by Büchi.^{5a} A particularly interesting variant of the Paterno–Büchi reaction is illustrated in

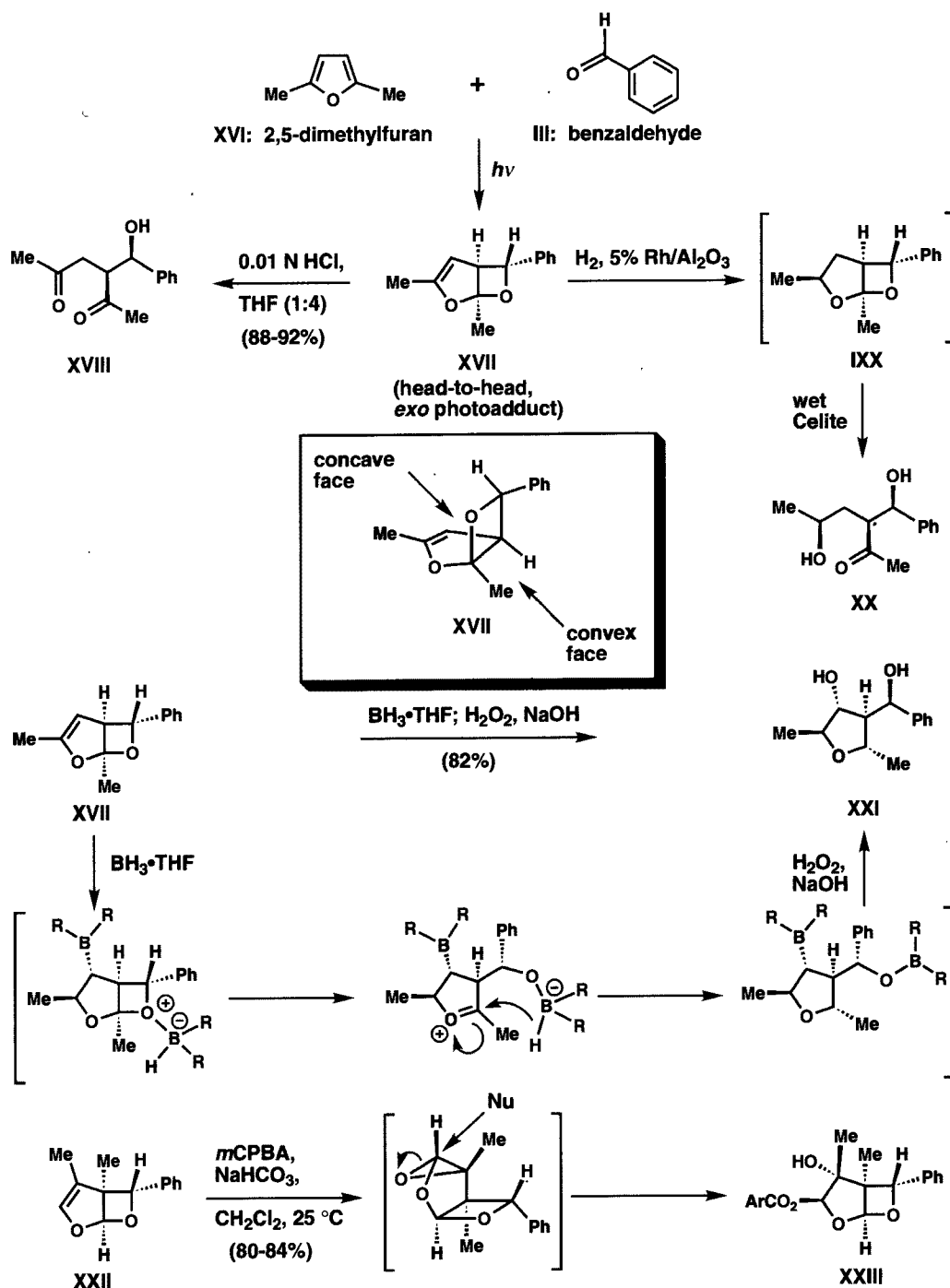


Scheme 2. The Paterno–Büchi reaction as a photochemical aldol equivalent.

Scheme 2. Irradiation of a mixture of acetone (XI) and ethyl vinyl ether (XII) is known to result in the formation of two regioisomeric oxetanes, intermediates XIII and XIV.⁹ Although a chemical yield of 60–70 % is very respectable, the regioselectivity for this transformation is low, as oxetanes XIII and XIV are produced in a ratio of approximately 3:7. Nevertheless, it is important to recognize that regioisomer XIII is simply a mixed cyclic acetal and should, therefore, be susceptible to hydrolysis. Indeed, exposure of the mixture of XIII and XIV to water at 25 °C accomplishes facile and selective hydrolytic opening of the four-membered heterocyclic ring of XIII and affords β -hydroxy aldehyde XV, together with unchanged XIV. Although the ubiquitous β -hydroxy carbonyl moiety is usually created through an aldol condensation, it is interesting to note that the combination of the Paterno–Büchi and hydrolysis reactions can provide an effective alternative. In certain contexts, the Paterno–Büchi reaction can be regarded as a photochemical aldol equivalent.

In the early 1980s, S.L. Schreiber and his group disclosed studies which provided the foundation for some elegant natural product syntheses.¹⁰ Encouraged by some important precedent provided by Sakurai in 1965,¹¹ Schreiber *et al.* reevaluated Paterno–Büchi photocycloaddition reactions between aldehydes and furans, and demonstrated that the resultant dioxabicyclo[3.2.0]heptene adducts are amenable to a variety of functionalization schemes¹² (see Scheme 3). In a representative example, irradiation of a mixture of 2,5-dimethylfuran (XVI) and benzaldehyde (III) results in the regio- and stereoselective formation of head-to-head *exo* photoadduct XVII. In all cases examined, the furan–aldehyde photocycloaddition step furnished only head-to-head regioisomers and exhibited a >20:1 preference for the *exo* diastereoisomer. Subjection of XVII to the action of 0.01 N HCl results in hydrolysis of the acid-labile internal ketal grouping and furnishes hydroxy diketone





Scheme 3. Stereoselective functionalizations of furan-aldehyde photoadducts.

XVIII in a yield of 88 to 92%. It is here that the relationship between the Paterno-Büchi photocycloaddition process and the aldol reaction is most readily apparent.

It is convenient, at this juncture, to address an important stereochemical issue. The suprafacial nature of the furan-aldehyde photocycloaddition event results in the formation of *cis*-fused photoadducts. An important consequence of a *cis* ring fusion within a structure is that molecules such as dioxabicyclo[3.2.0]heptene XVII possess a folded molecular framework that is distinguished by a hindered concave face and a relatively unhindered convex face (see insert in Scheme 3).¹³ The folded or cup-shaped geometry of XVII would thus be expected to impose strict control over the stereochemical course of operations carried out on its periphery. Indeed, under an atmosphere of hydrogen and in the presence of 5% Rh/Al₂O₃, the enol ether double bond in XVII is saturated in a completely diastereoselective manner producing compound XX via the labile ketal oxetane IXX. The stereochemical course of the hydrogenation step is consistent with a convex face addition of a molecule of hydrogen to XVII.

Stereoselective oxidations of the dioxabicyclo[3.2.0]heptene adducts were also found to be feasible. For example, treatment of XVII with borane-THF complex affords, after oxidative workup with basic hydrogen peroxide, intermediate XXI in 82% yield (see Scheme 3). Interestingly, reduction of the internal ketal, with retention of configuration, occurs in addition to double bond hydroboration. As expected, hydroboration/oxidation of the enol ether double bond in XVII, the equivalent of an anti-Markovnikov hydration reaction,¹⁴ takes place from the less hindered convex face of the molecule and results in the formation of two additional stereocenters. To account for the observed ketal reduction, it is important to recall the Lewis-acidic properties of borane (BH₃). It is conceivable that borane induces opening of the internal ketal grouping, in the manner illustrated in Scheme 3, and affords intermediate XXI after a directed internal delivery of hydride¹⁵ and oxidative workup. It is most impressive that intermediate XXI, a substance which harbors five contiguous stereocenters, is created in only two steps from simple, achiral starting materials.

The enol ether double bond contained within the *cis*-fused dioxabicyclo[3.2.0]heptene photoadducts can also be oxidized, in a completely diastereoselective fashion, with *m*CPBA. Treatment of intermediate XXII, derived in one step from a Paterno-Büchi reaction between 3,4-dimethylfuran and benzaldehyde, with *m*CPBA results in the formation of intermediate XXIII. Once again, consecutive photocycloaddition and oxidation reactions furnish a highly oxygenated system that possesses five contiguous stereocenters, one of which is quaternary. Intermediate XXIII is particularly interesting because its constitution and its relative stereochemical relationships bear close homology to a portion of a natural product known as asteltoxin.

The toxic maize cultures of *Aspergillus stellatus* contain a mycotoxin that exerts a potent inhibitory effect on the adenosinetriphosphatase activity of *Escherichia coli* BF₁.¹⁶ This mycotoxin was isolated by Vleggaar *et al.* in the late 1970s and was given the name asteltoxin. On the basis of spectroscopic data and an X-ray crystallographic analysis, these investigators were able to establish that structure **1** correctly depicts the constitution and relative stereochemistry of asteltoxin. Asteltoxin (**1**) is a trienic α -pyrone that bears a close structural relationship to aurovertin¹⁷ and citreoviridin,¹⁸ known inhibitors of oxidative phosphorylation.

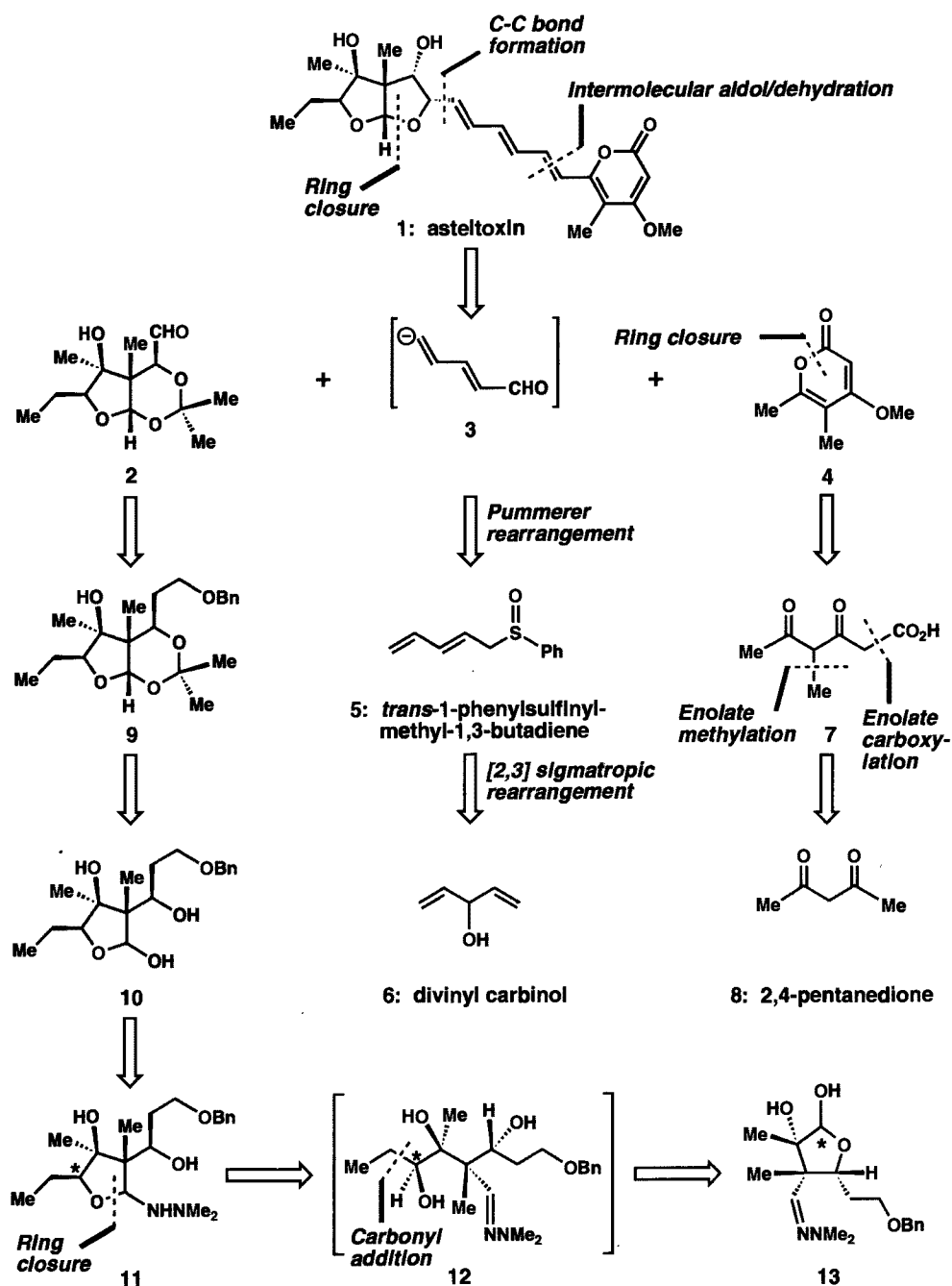
The asteltoxin molecule is highly oxygenated and complex; its dioxabicyclo[3.3.0]octane frame is distinguished by six contiguous stereogenic centers, one of which is quaternary. Interestingly, it has been demonstrated that this highly oxygenated bicyclic substructure is responsible for the inhibition and binding properties of asteltoxin.¹⁹ The remainder of this chapter will be devoted to Schreiber's total synthesis of asteltoxin (**1**).^{10,20}

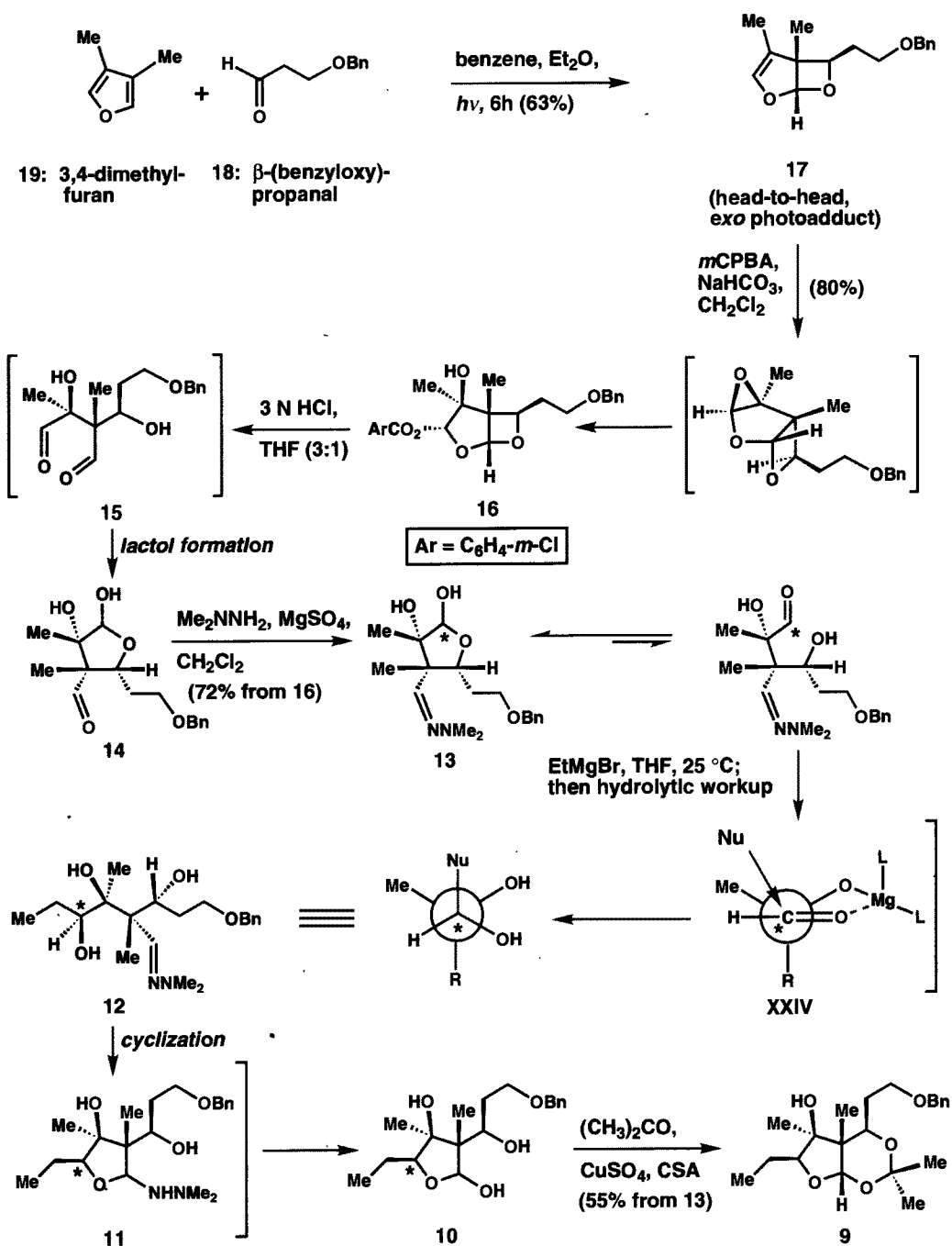
20.2 Retrosynthetic Analysis and Strategy

The general features of this elegant and efficient synthesis are illustrated, in retrosynthetic format, in Scheme 4. Asteltoxin's structure presents several options for retrosynthetic simplification. Disassembly of asteltoxin in the manner illustrated in Scheme 4 furnishes intermediates **2–4**. In the synthetic direction, attack on the aldehyde carbonyl in **2** by anion **3** (or its synthetic equivalent) would be expected to afford a secondary alcohol. After acid-catalyzed skeletal reorganization, the aldehydic function that terminates the doubly unsaturated side chain could then serve as the electrophile for an intermolecular aldol condensation with α -pyrone **4**. Subsequent dehydration of the aldol adduct would then afford asteltoxin (**1**).

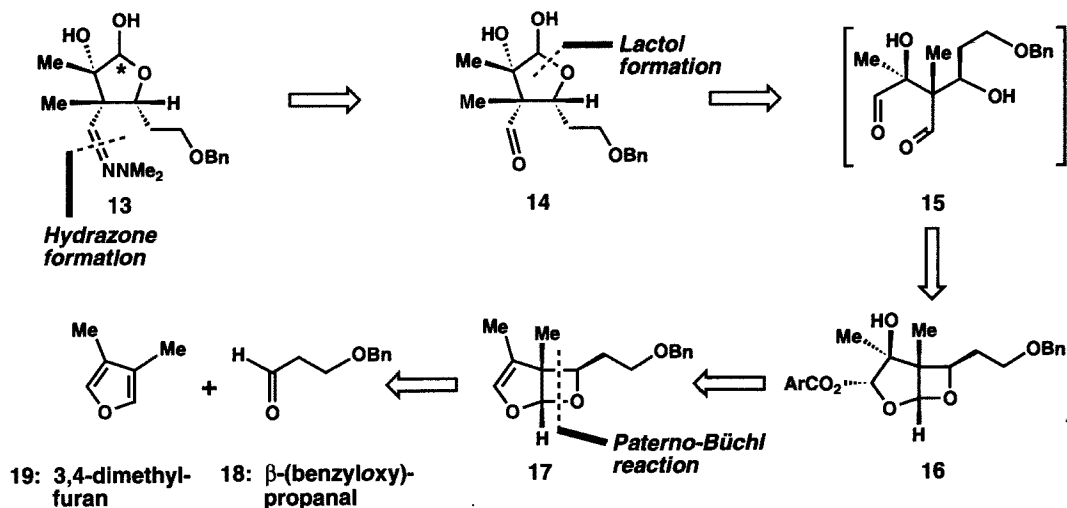
The synthetic challenge is now reduced to the preparation of intermediates **2–4**. Although intermediates **3** and **4** could potentially be derived in short order from very simple precursors (see Scheme 4), intermediate **2** is rather complex, particularly with respect to stereochemistry. Through a short sequence of conventional functional group manipulations, it is conceivable that aldehyde **2** could be derived from intermediate **9**. Hydrolysis and ketalization reactions could then permit the formation of **9** from intermediate **11**, the cyclic hemiaminal of the highly stereo-defined acyclic molecule, intermediate **12**.

Although it may not be obvious, putative intermediate **12** could conceivably be fashioned in one step from lactol **13**. Of course, **13** can be regarded as a latent aldehyde that should be amenable to an α -chelation-controlled carbonyl addition reaction²¹ with ethylmagnesium bromide. This event could secure the formation of the indicated stereocenter in intermediate **12**. It seems reasonable to suppose that the sequential action of aqueous acid and 1,1-

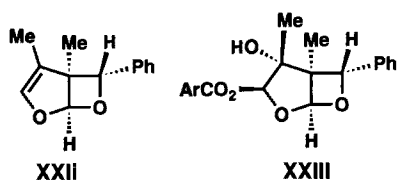
**Scheme 4.** Retrosynthetic analysis of asteltoxin (1).



Scheme 5. Synthesis of intermediate 9.

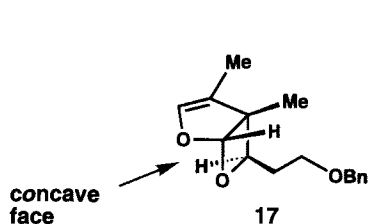


Scheme 4. Retrosynthetic analysis of asteltoxin (**1**) (continued).

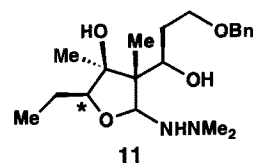
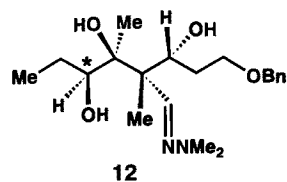
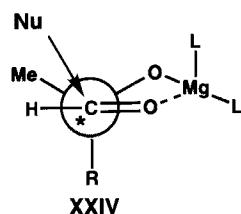
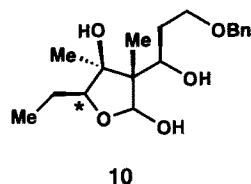
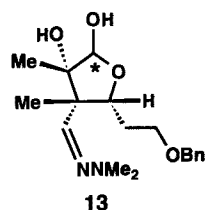
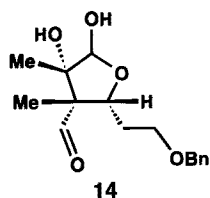
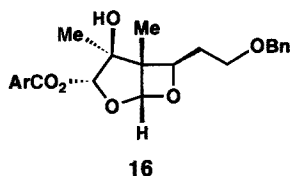


dimethylhydrazine on dioxabicyclo[3.2.0]heptane **16** would result in the formation of lactol hydrazone **13** via intermediates **15** and **14** (see Scheme 4). On the basis of the model studies illustrated in Scheme 3, and the conversion of intermediate XXII to XXIII, in particular, the prospects for achieving a completely diastereoselective oxidation of **17** to give **16** seem excellent. Dioxabicyclo[3.2.0]heptene **17**, the host of three contiguous stereocenters, could conceivably be derived in a single step through a Paterno-Büchi photocycloaddition between β -(benzyloxy)-propanal (**18**) and 3,4-dimethylfuran (**19**).

20.3 Total Synthesis



Our journey begins with the photo-induced union of 3,4-dimethylfuran (**19**) and β -(benzyloxy)-propanal (**18**) (see Scheme 5). Irradiation of a solution of these two simple, achiral compounds in benzene with a 450 W Hanovia lamp equipped with a vycor filter results in the exclusive formation of head-to-head, *exo* photoadduct **17** in 63 % yield. As a *cis*-fused dioxabicyclo[3.2.0]heptene system, intermediate **17** possesses a folded molecular framework to which access is obstructed on the concave face. In the presence of *m*CPBA, the less hindered convex face of the enol ether double bond is oxidized in a completely diastereoselective fashion, affording intermediate **16** in 80 % yield after regioselective opening of

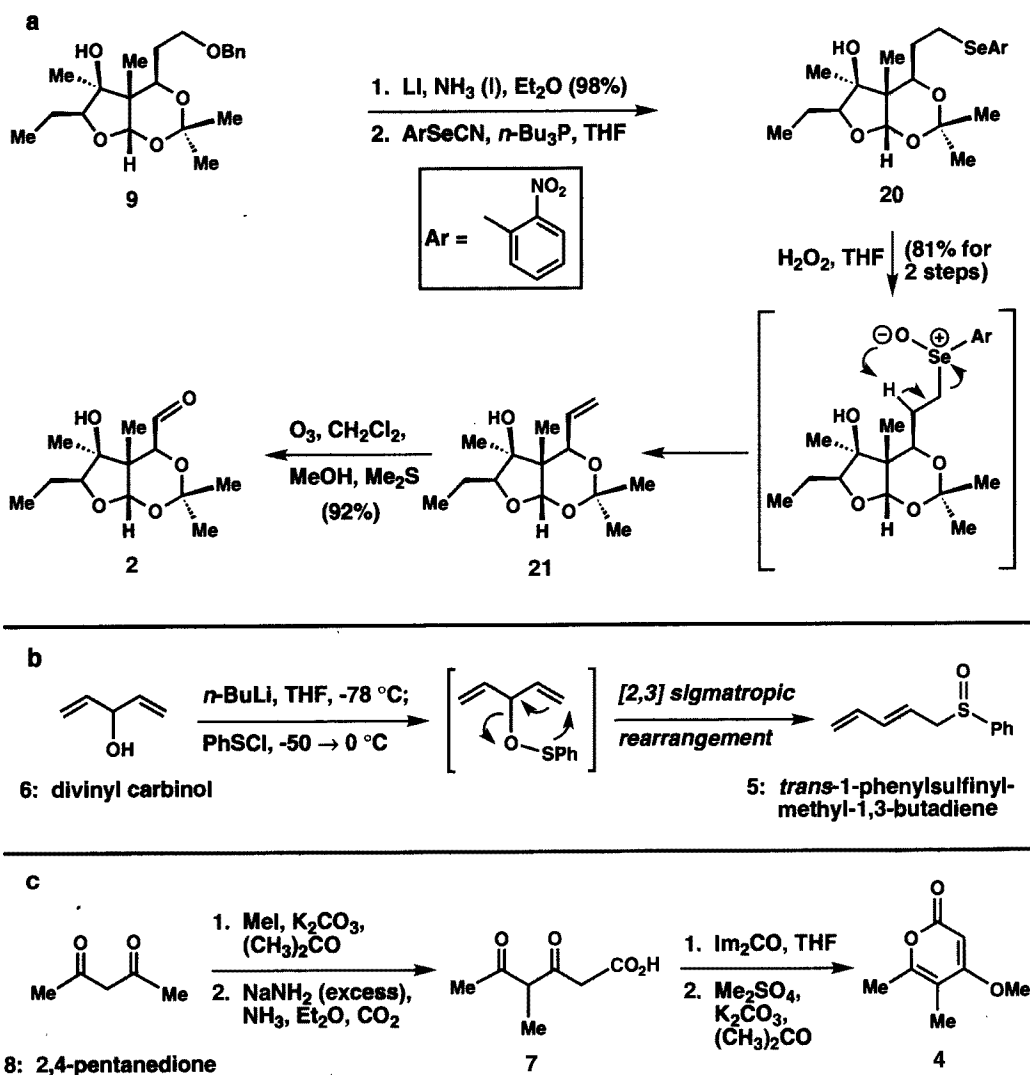


the oxirane ring with *meta*-chlorobenzoate. For convenience, the *m*CPBA oxidation reaction was performed immediately after the photocycloaddition step. It is noteworthy that multigram quantities of **16**, a functionalized and stereochemically complex substance, can be procured by this simple two-step reaction sequence.

Subjection of intermediate **16** to the action of 3 *N* aqueous HCl in THF results in the formation of monocyclic lactol **14**. In the presence of aqueous acid, the internal acetal grouping in intermediate **16** is hydrolyzed and lactol **14** is produced after the liberated secondary hydroxyl group attacks the terminal aldehyde carbonyl positioned five atoms away (see intermediate **15**). Protection of the free aldehyde function in **14** with 1,1-dimethylhydrazine proceeds smoothly under dehydrating conditions and affords intermediate **13** in an overall yield of 72 %.

Although the intramolecular attack of a hydroxyl group on a proximal aldehyde carbonyl effects the virtual saturation of the latter, it is important to recognize that the lactol grouping is really just a latent aldehyde; the lactol and the open hydroxy aldehyde forms are active participants in a ring-chain equilibrium. Treatment of lactol **13** with several equivalents of ethylmagnesium bromide results in the formation of **10** after hydrolytic workup, and presumably through the processes illustrated in Scheme 5. This interesting stereocontrolled transformation begins with an acid-base reaction between **13** and ethylmagnesium bromide that affords a tertiary magnesium alkoxide which can participate in the formation of a five-membered chelate with the adjacent aldehyde carbonyl (see intermediate XXIV in Scheme 5). Internal chelation of the type illustrated in XXIV activates the aldehyde carbonyl for a nucleophilic attack by an additional equivalent of ethylmagnesium bromide, an event which takes place with preference for the more accessible *Si* diastereoface, affording **12** as a transient intermediate after aqueous quenching. Inspection of the constitution of intermediate **12** reveals that only three atoms intervene between the newly formed secondary hydroxyl group (see C*) and a suitably electrophilic carbon-nitrogen double bond, a circumstance that should permit spontaneous cyclization to intermediate **11**. The conversion of **11** to **10** during aqueous workup is unexceptional and does not merit special comment. On the other hand, it is conceivable that the dimethylhydrazone group in **12** undergoes conversion to the corresponding aldehyde during hydrolytic workup, after which cyclization occurs to give **10**.

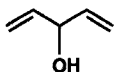
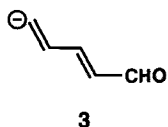
The completion of the synthesis of key intermediate **2** requires only a straightforward sequence of functional group manipulations. In the presence of acetone, cupric sulfate, and camphorsulfonic acid (CSA), the lactol and secondary hydroxyl groups in **10** are simultaneously protected as an acetonide (see intermediate **9**). The overall yield of **9** is 55 % from **13**. Cleavage of the benzyl ether in **9** with lithium metal in liquid ammonia furnishes a diol (98 % yield) which is subsequently converted to selenide **20** according to Grieco's procedure²² (see Scheme 6a). Oxidation of the selenium atom



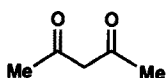
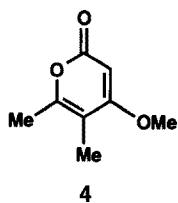
Scheme 6. Synthesis of intermediates **2** (a), **5** (b), and **4** (c).

in **20** with hydrogen peroxide furnishes the corresponding selenoxide which undergoes conversion to alkene **21** through *syn*-elimination (81 % yield for two steps). Oxidative cleavage of the monosubstituted double bond in **21** with ozone affords key intermediate **2** in an excellent yield of 92 %.

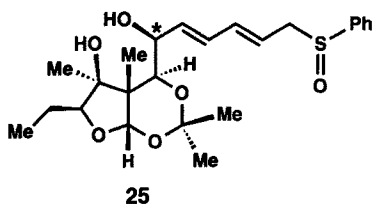
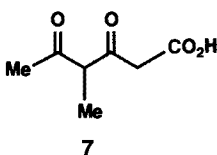
The elaboration of the polyunsaturated side chain of asteltoxin requires a stereoselective coupling of aldehyde **2** with a suitable synthetic equivalent for the anion of 4-formyl-1,3-butadiene (see intermediate **3** in Scheme 4). Acid-induced skeletal reorganization of the aldehyde addition product, followed by an intermolecular



6: divinyl carbinol



8: 2,4-pentanedione

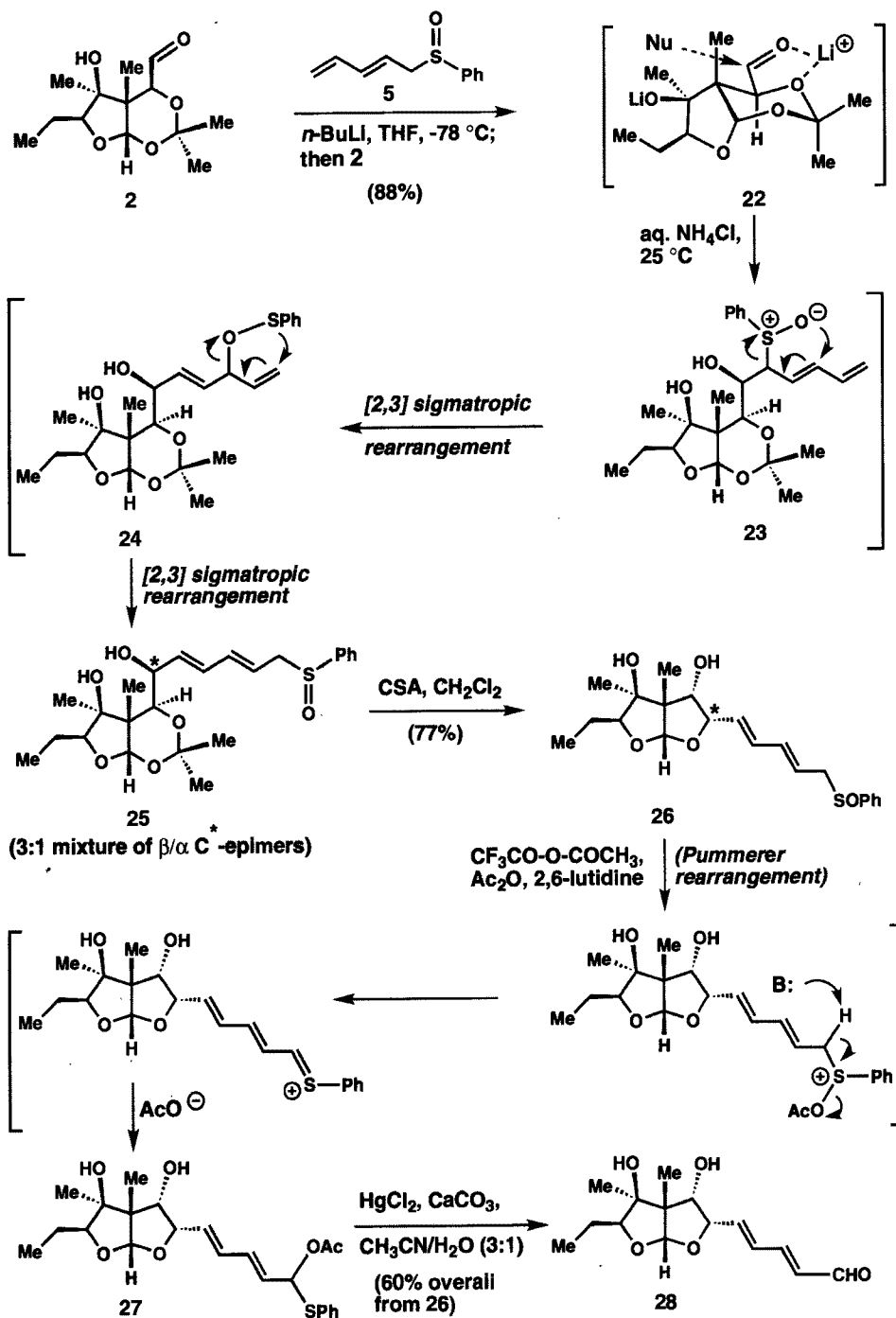


aldol condensation between the resultant dienic aldehyde and pyrone **4** and dehydration would complete the synthesis of asteltoxin. During the course of a total synthesis of 5-desoxyeukotriene D, Corey and coworkers discovered that the conjugate base of *trans*-1-phenylsulfinylmethyl-1,3-butadiene (**5**) is a valuable synthetic equivalent for the anion of 4-formyl-1,3-butadiene (**3**).²³ Alkylation of the sulfoxide-stabilized anion derived from **5** with a suitable electrophile, followed sequentially by two consecutive [2,3] sigmatropic rearrangements (for example, see **2** → **25** in Scheme 7) and a Pummerer rearrangement²⁴ (see **26** → **28** in Scheme 7), could result in the formation of the desired dienal. The synthesis of sulfoxide **5** could be achieved in a single step from divinyl carbinol (**6**) through a sulfenate-to-sulfoxide rearrangement²⁵ (see Scheme 6b).

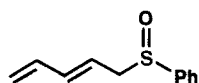
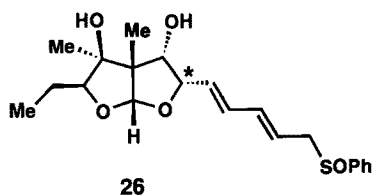
The straightforward construction of substituted pyrone **4** proceeded as follows (see Scheme 6c). Alkylation of the monoanion of 2,4-pentanedione (**8**) with methyl iodide furnishes 3-methyl-2,4-pentanedione. Conversion of this substance into the corresponding dianion with sodium amide followed by selective carboxylation of the more basic site provides intermediate **7**. Pyrone **4** is obtained after cyclization with 1,1'-carbonyldiimidazole and methylation of the resulting enol with dimethyl sulfate.

Now that key intermediate **2** and a suitable synthetic equivalent of anion **3** are available, the stage is set for the elaboration of the unsaturated side chain of asteltoxin (see Scheme 7). Treatment of aldehyde **2** with the resonance-stabilized carbanion derived from the action of *n*-butyllithium on sulfoxide **5** at -78°C results in the formation of a key carbon-carbon bond. After quenching of the reaction mixture with aqueous ammonium chloride, the resultant suspension is allowed to warm to 25°C during which time the β -hydroxy sulfoxide addition product **23** undergoes conversion to intermediate **25** through consecutive [2,3] sigmatropic rearrangements (see **23** → **24** → **25**, Scheme 7). Intermediate **25** is produced in 88% yield as a 3:1 mixture of diastereoisomers, epimeric at C*, in favor of the β -isomer. Intermediate **25** could be obtained in pure form after silica gel chromatography. The preferred stereochemical course for the carbonyl addition step is consistent with an α -chelation-controlled²¹ addition of the sulfoxide-stabilized carbanion to the *Si* diastereoface of the aldehyde carbonyl (see intermediate **22**, Scheme 7).

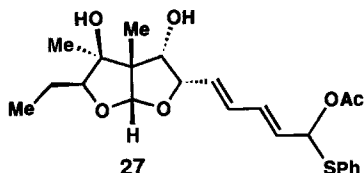
Contained within intermediate **25** is an acid-labile mixed acetal group and it was found that treatment of **25** with camphorsulfonic acid (CSA) results in the formation of dioxabicyclo[3.3.0]octane **26** in 77% yield. Acid-induced cleavage of the mixed cyclic acetal function in **25**, with loss of acetone, followed by intramolecular interception of the resultant oxonium ion by the secondary hydroxyl group appended to C* leads to the observed product. Intermediate **26** clearly has much in common with the ultimate target molecule. Indeed, the constitution and relative stereochemistry of the dioxabicyclo[3.3.0]octane framework in **26** are identical to the corresponding portion of asteltoxin.



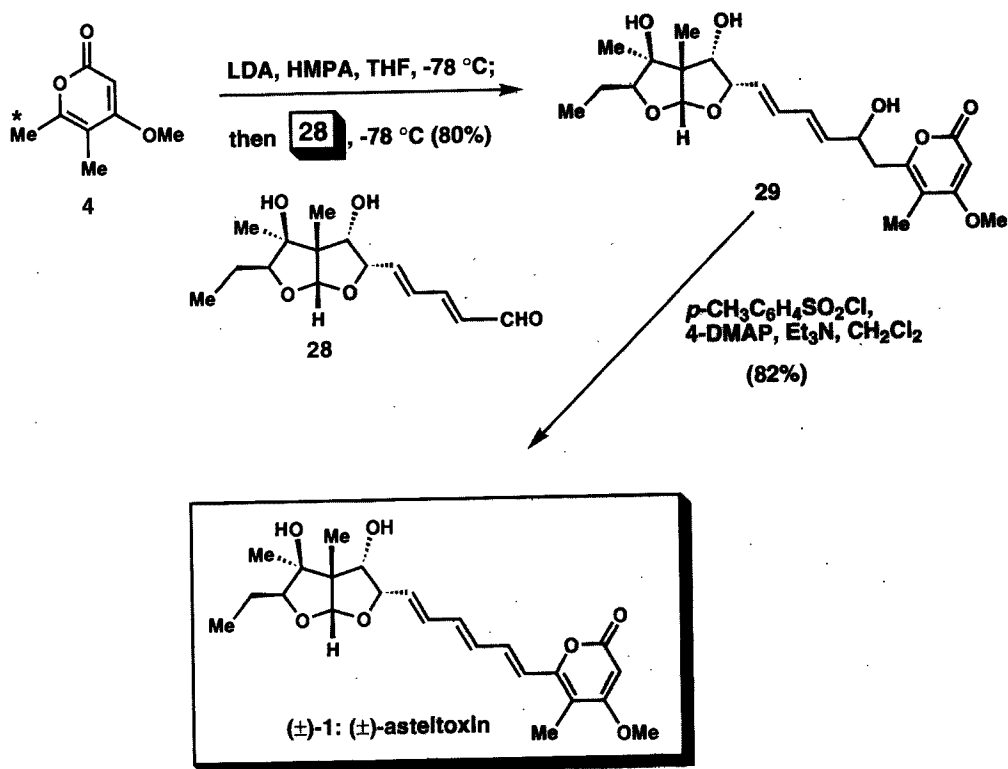
Scheme 7. Synthesis of intermediate 28.



5: *trans*-1-phenylsulfinyl-methyl-1,3-butadiene



It is instructive, at this stage, to draw attention to the sulfoxide grouping in intermediate **26**. As we have already witnessed, the versatile sulfoxide functional group permitted the conversion of intermediate **5** into a resonance-stabilized carbanion which was used to form a key carbon-carbon bond, and it permitted the elaboration of a significant portion of asteltoxin's unsaturated side chain through sequential [2,3] sigmatropic rearrangements. In addition, the sulfoxide function is a viable precursor for an electrophilic carbonyl group. Acetylation of the sulfoxide oxygen in **26**, under the conditions illustrated in Scheme 7, initiates a Pummerer rearrangement²⁴ and leads to the formation of acetoxysulfide **27**, a substance which was taken forward in crude form. The combined action of mercury(II) chloride and calcium carbonate on a solution of **27** in aqueous acetonitrile unveils the reactive dienal moiety (see **28**) and sets the stage for the crucial intermolecular aldol condensation with substituted pyrone **4**. Deprotonation of the indicated methyl group (C*) in **4** with lithium diisopropylamide (LDA) furnishes a delocalized anion, an extended enolate, which reacts smoothly with aldehyde **28** to give aldol adduct **29** in a yield of 80% (see Scheme 8). Tosylation of the less hindered secondary allylic hydroxyl group in **29** with concomitant elimination completes Schreiber's elegant synthesis of (±)-asteltoxin [(±)-**1**].



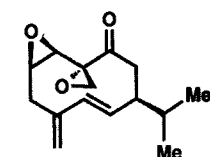
Scheme 8. Synthesis of (±)-asteltoxin (**1**) [(±)-**1**].

20.4 Conclusion

Since its discovery in 1909,⁴ the process now known as the Paterno–Büchi reaction has evolved into a powerful tool for the elaboration of highly oxygenated and stereochemically complex molecules. The relationship of the Paterno–Büchi reaction to the classic aldol condensation is particularly interesting. In certain circumstances, the use of the Paterno–Büchi reaction as a photochemical aldol equivalent can provide access to β -hydroxy carbonyl compounds that could not be efficiently prepared through a direct aldol condensation.^{9,12} The feasibility of conducting Paterno–Büchi photocycloaddition reactions between furans and aldehydes was first demonstrated by Sakurai in the 1960s.¹¹ Inspired by the impressive regio- and diastereoselectivities that typically attend such photocycloaddition reactions,^{11,26} Schreiber and his colleagues dramatically extended the utility of furan–aldehyde Paterno–Büchi reactions for the synthesis of complex natural products.¹⁰ The photo-induced union of simple, achiral furans and aldehydes furnishes a dioxabicyclo[3.2.0]heptene photoadduct that can serve as a valuable template for the creation of stereogenic centers. As we have seen, the formation of *cis*-fused dioxabicyclo[3.2.0]heptene photoadducts is a natural consequence of the suprafacial nature of the furan–aldehyde [2+2] cycloaddition. The folded or cup-shaped molecular frameworks of these photoadducts are distinguished by a convex face and a considerably more hindered concave face (see Scheme 3). As demonstrated by Schreiber *et al.*, this valuable substrate structural feature permits highly diastereoselective operations to be carried out on the remaining site of unsaturation. Perhaps the most impressive feature of Schreiber's synthesis of asteltoxin is the speed with which vicinal stereochemical relationships are secured, in short order, through a sequence of reactions in which the furan–aldehyde Paterno–Büchi photocycloaddition plays a commanding role.

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1: periplanone B

S. L. Schreiber (1984)

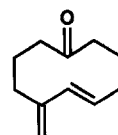
Periplanone B

21.1 Introduction

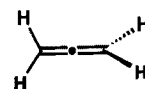
In 1981, Schreiber and Santini disclosed the application of a consecutive oxy-Cope rearrangement/cyclobutene ring opening sequence to the synthesis of a cyclodecadienone (see intermediate **8**, Scheme 1) that bears a close resemblance to the parent framework of germacranoid natural products such as periplanone B (**1**).¹ Schreiber's elegant strategy commences with a [2+2] photocycloaddition reaction² between allene (**2**) and a cyclohexenone (**3**) results in the completely regioselective formation of head-to-head photoadduct (\pm)-**4** (for clarity only one enantiomer is illustrated). The observed regiochemical course for this reaction was actually anticipated on the basis of Corey's pioneering studies.³ Using light, one of the simplest means of effecting a chemical reaction, this [2+2] cycloaddition process accomplishes the simultaneous introduction of two contiguous stereocenters and a new four-membered ring.

By virtue of its *cis* ring fusion, bicyclic β,γ -unsaturated ketone **4** possesses a folded molecular framework which is distinguished by a hindered concave face and a more accessible convex face.⁴ This architectural feature offers unique opportunities for controlling the stereochemical course of reactions carried out on **4**. For example, the attack of vinylmagnesium bromide upon the ketone carbonyl in **4** proceeds diastereoselectively, providing divinylcyclohexanol **5** in 79 % yield; the folded geometry of **4** compels the Grignard reagent to add to the less hindered side of the molecule.

As shown by Marvell and Whalley in 1970,⁵ divinylcyclohexanols, resulting from the reaction of a vinyl organometallic reagent



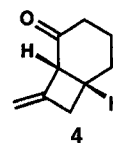
trans-8



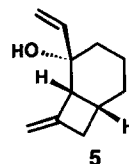
2: allene



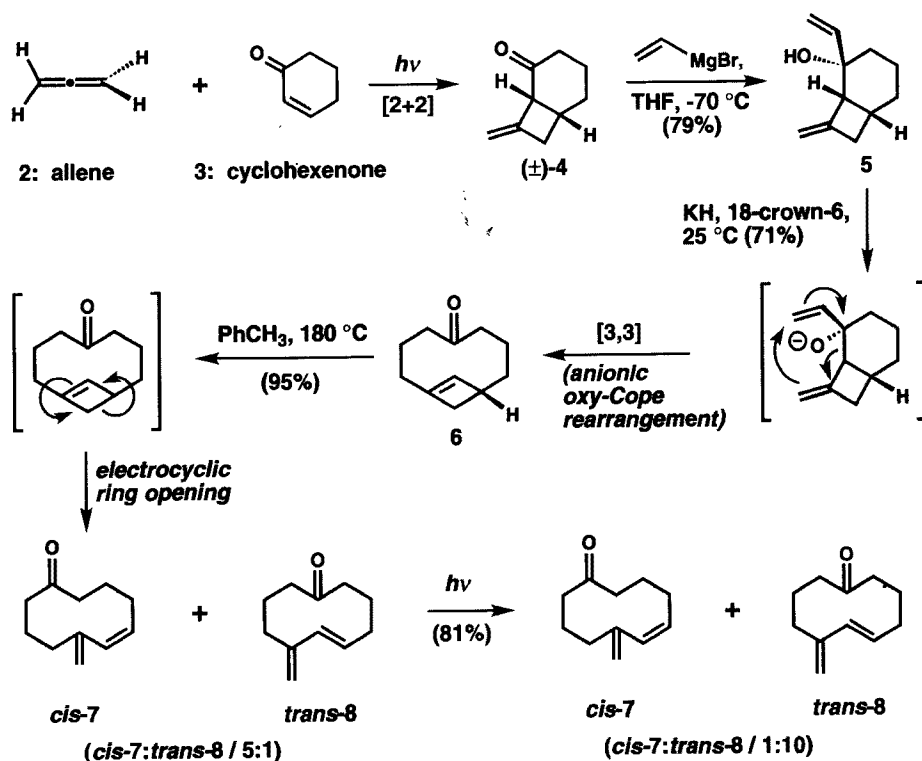
3: cyclohexenone



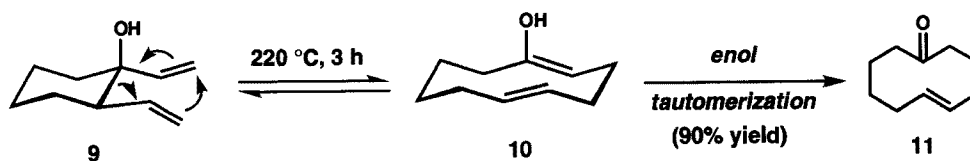
4



5



Scheme 1. Schreiber's oxy-Cope rearrangement/cyclobutene ring opening strategy for the synthesis of cyclodecadienone **8**.



Scheme 2. Oxy-Cope rearrangement of *trans* 1,2-divinylcyclohexanol (**9**).

with a β,γ -unsaturated cyclohexenone, can serve as viable substrates for thermally induced oxy-Cope rearrangements (see Scheme 2). In organic synthesis, this particular type of transformation is very valuable, for it provides efficient access to strained cyclodecenones. It is important to note that the ring of oxy-Cope substrate **9** is expanded by four carbon atoms on [3,3] sigmatropic rearrangement, and that facile tautomerization of the ring-expanded enol **10** to the corresponding ketone renders the process irreversible. The exclusive formation of *trans* 5-cyclodecen-1-one (**11**) is a natural consequence of a chairlike transition state geometry for the sigmatropic event.

In the case at hand, it was anticipated that divinylcyclohexanol **5** could be induced to undergo an oxy-Cope rearrangement to give the isomeric cyclobutene bridgehead olefin **6** (see Scheme 1). Although attempts to accomplish this transformation thermally were completely unsuccessful, it was found that compound **6** can be produced in 71 % yield simply by treating divinylcyclohexanol **5** with potassium hydride and 18-crown-6 in THF at 25 °C. Under these conditions, the deprotonation of **5** by KH affords the corresponding alkoxide which subsequently participates in a charge-accelerated, anionic oxy-Cope rearrangement.^{6,7} The induction of a [3,3] sigmatropic rearrangement by deprotonating an oxy-Cope substrate was first demonstrated by Evans and Golob.⁶ The facility of the sigmatropic isomerization of **5** to **6** is remarkable in view of the fact that the geometry of **5** does not appear to permit efficient orbital overlap.

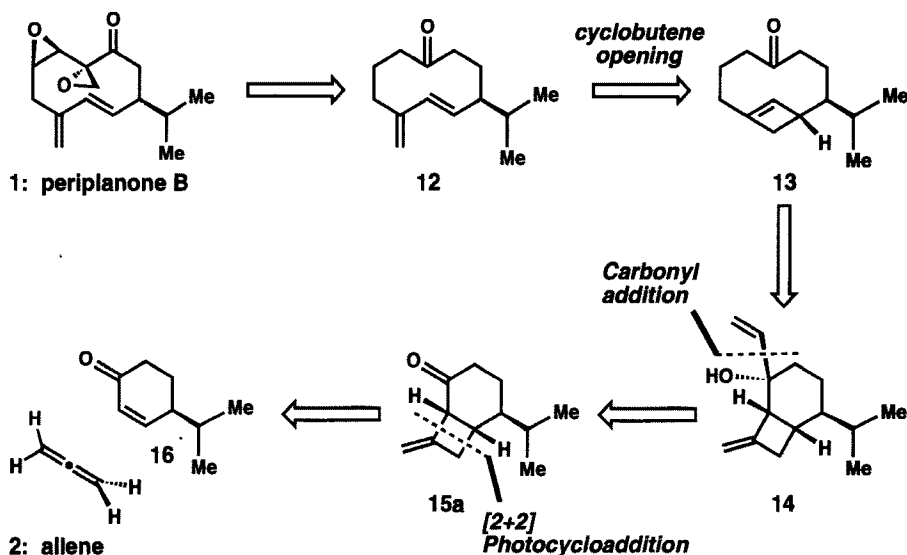
Compound **6** is a pivotal intermediate in Schreiber's synthesis. It was hoped that the conspicuous and strained bridgehead cyclobutene substructure in **6** would undergo a conrotatory electrocyclic ring opening upon thermolysis to give an isomeric 1,3-diene (**8**, Scheme 1). In the event, when a solution of cyclobutene **6** in toluene is confined to a sealed tube and heated to 180 °C for 12 h, a stereoisomeric mixture of 1,3-dienes **7** and **8** is produced in an excellent yield of 95 % (**7**:**8** ca. 5:1). Finally, irradiation of the 5:1 mixture of *cis*-**7** and *trans*-**8**, or of each independently, establishes a photostationary state in which the desired *trans* isomer **8** predominates (**8**:**7** ca. 10:1).

Based on the successful series of transformations summarized in Scheme 1, Schreiber and Santini developed an efficient and elegant synthesis of periplanone B (**1**),⁸ the potent sex pheromone of the American cockroach, *Periplaneta americana*. This work constitutes the second total synthesis of periplanone B, and it was reported approximately five years after the landmark periplanone B synthesis by W.C. Still⁹ (see Chapter 13). As in the first synthesis by Still, Schreiber's approach to periplanone B takes full advantage of the facility with which functionalized 5-cyclodecen-1-one systems can be constructed via anionic oxy-Cope rearrangements of readily available divinylcyclohexanols.^{5,7} In addition, both syntheses of periplanone B masterfully use the conformational preferences of cyclodecanoid frameworks to control the stereo- and regiochemical course of reactions carried out on the periphery of such ring systems.¹⁰

21.2 Retrosynthetic Analysis and Strategy

The key features of Schreiber's total synthesis of periplanone B (**1**) are outlined retrosynthetically in Scheme 3. Cyclodecadienone **12** presents itself as a key synthetic intermediate; it was projected that a synthesis of periplanone B could be achieved in the event that **12** can be oxidatively functionalized in a regio- and stereocontrolled fashion. You will note that compound **12** possesses the basic skeleton characteristic of the germacranes class of natural products and that its structure is very similar to the *trans* cyclodecadienone prepared previously in the model study described in Scheme 1. A most elegant feature of Schreiber's strategy is the recognition that a bridgehead cyclobutene can serve as a masking device for the conjugated 1,3-diene moiety of the natural product. It was anticipated that thermolysis of bicyclic bridgehead olefin **13** would induce electrocyclic ring opening to give compound **12**. The strained bridgehead cyclobutene ring of **13** can thus be regarded as a latent 1,3-diene.

The 1,5 relationship between the olefin and keto groups in **13** satisfies the structural prerequisite for the oxy-Cope transform,¹¹ and, like the first synthesis of periplanone B by Still,⁹ Schreiber's strategy recognizes that an anionic oxy-Cope rearrangement could provide a powerful and direct method for the assembly of cyclodecenone **13**. On the basis of the model study described previously, it was projected that deprotonation of the free hydroxyl group in **14**



Scheme 3. Schreiber's retrosynthetic analysis of periplanone B (**1**).

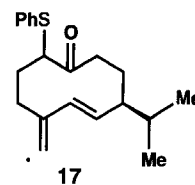
would initiate the desired sigmatropic ring expansion process to give **13**; with a felicitously placed carbon–carbon double bond, **13** could then serve as the immediate precursor of key intermediate **12**. Retrosynthetic cleavage of the indicated bond in **14** provides *cis*-fused bicyclic ketone **15a** as a potential precursor. The latter substance could, in turn, be fashioned in one step by an intermolecular [2+2] photocycloaddition reaction between substituted cyclohexenone **16** and allene (**2**). The reduction of this promising plan to practice is addressed in Schemes 4 and 5.

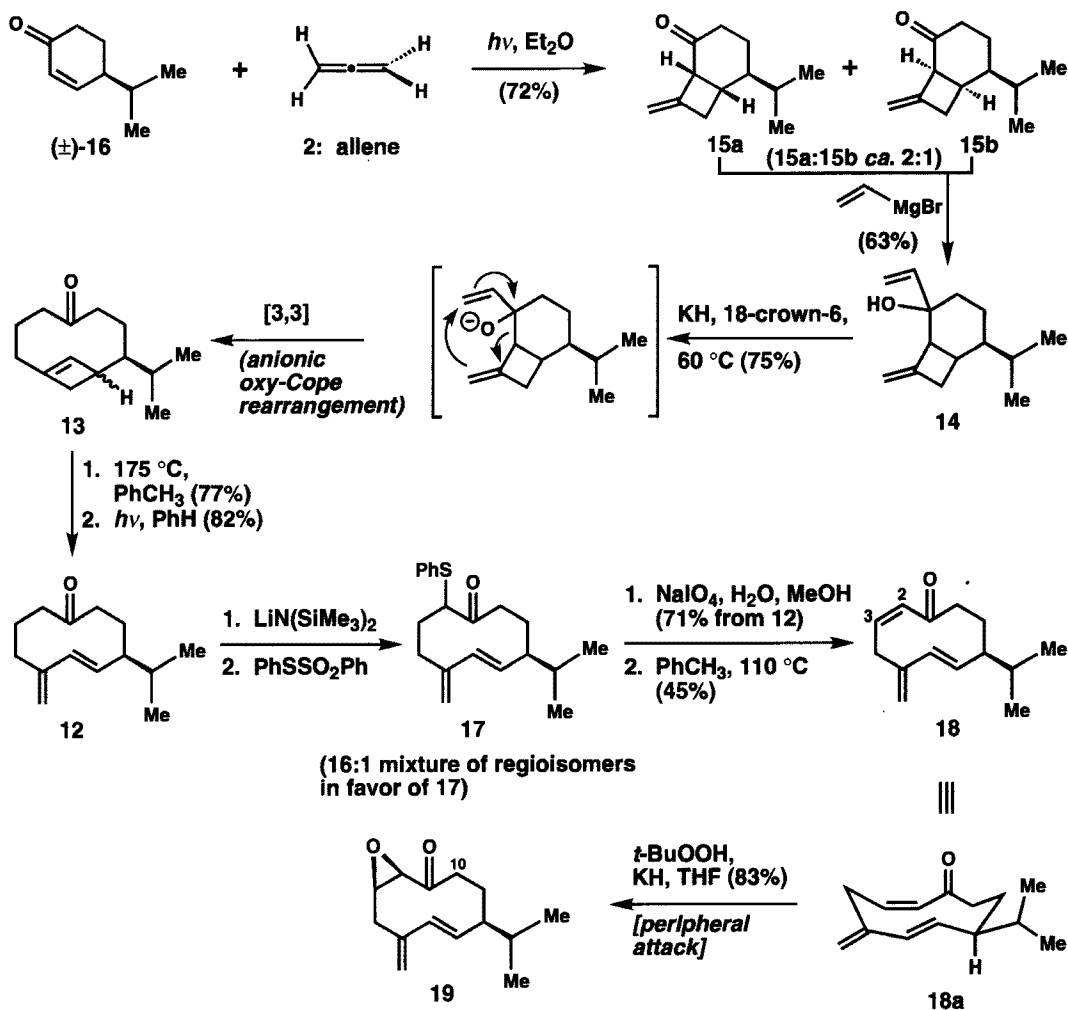
21.3 Total Synthesis

Schreiber's synthesis of periplanone B commences with a [2+2] photocycloaddition reaction between racemic 4-isopropyl-2-cyclohexen-1-one (**16**) and allene (**2**) to give approximately a 2:1 mixture of the *anti* (**15a**) and *syn* (**15b**) head-to-head³ photoadducts in a combined yield of 72 % (see Scheme 4). This productive transformation creates two new carbon–carbon bonds and an appropriately functionalized four-membered ring. Although compounds **15a** and **15b** can be obtained in pure form, careful purification at this stage was deemed unnecessary because both **15a** and **15b** can be converted into the same *trans* butadiene **12**. The formation of diastereomeric photoadducts in this reaction is of no consequence since the two ring-fusion stereocenters in **15a** and **15b** are eventually converted to achiral, trigonal centers. As expected, a completely diastereoselective 1,2-addition of vinylmagnesium bromide to the ca. 2:1 mixture of **15a** and **15b** affords a ca. 2:1 mixture of allylic alcohols **14** in a yield of 63 %. In this reaction, vinylmagnesium bromide adds in a completely diastereoselective fashion to the less congested convex faces of **15a** and **15b**.

When a solution of **14** in THF is heated to 60 °C in the presence of potassium hydride and 18-crown-6, the hydroxyl group is deprotonated and the resultant alkoxide accelerates an oxy-Cope ring-expansion process to give the expected 2:1 mixture of bicyclic bridgehead olefins **13** in a very satisfactory yield of 75 %. Thermolysis (175 °C) of **13** induces electrocyclic ring opening and furnishes a mixture of the desired *trans* diene **12** and the undesired *cis* diene isomer. Although these substances can be isolated in pure form, irradiation of the mixture of isomeric dienes establishes a photostationary equilibrium consisting of a 15:1 mixture enriched in the *trans* isomer. In this way, the desired *trans* diene **12** can be obtained in a yield approaching 75 %.

From intermediate **12**, the path to periplanone B (**1**) is short but interesting. Enolization of **12** with lithium bis(trimethylsilyl)amide at –78 °C, followed by sulfenylation using Trost's reagent,¹² affords a 16:1 mixture of regioisomeric monosulfenylated ketones favoring intermediate **17**. The regioselectivity displayed in this reaction is





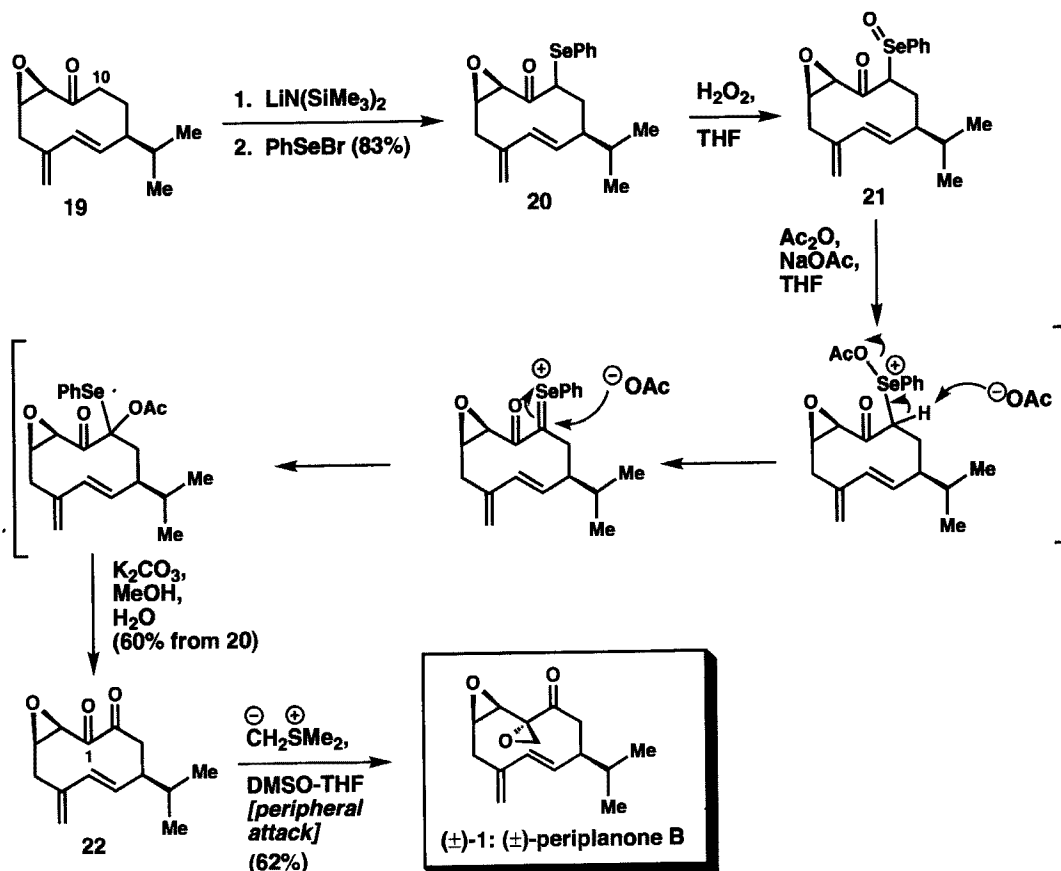
Scheme 4. Synthesis of intermediate 19.

interesting and no doubt intimately related to the conformational properties of intermediate **12**.^{9,10} Separation of **17** from the regioisomeric impurity is not necessary because the sulfoxide derived from **17** is eliminated readily on heating to give *cis* enone **18**, while the sulfoxide derived from the minor regioisomer of **17** is recovered unchanged. In the event, oxidation of the 16:1 regioisomeric mixture of sulfides with sodium periodate, followed by pyrolysis (110 °C), results in the formation of *cis* enone **18** in 32% yield based on intermediate **12**.

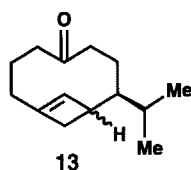
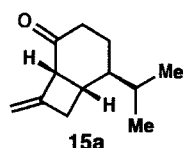
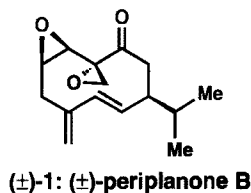
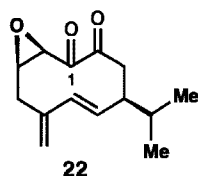
On the basis of precedent established previously by Still,⁹ the C2–C3 enone double bond in **18** is stereoselectively oxidized with potassium *tert*-butylperoxide to give a 4:1 mixture of stereois-

meric epoxides, favoring intermediate **19**. It is instructive to recall that the preference for an *s-trans* diene configuration favors the adoption of conformation **18a** (Scheme 4). This conformational preference, together with the established tendency for a peripheral attack by the oxidant, leads to the formation of **19**.⁹

An important task remaining is the introduction of a ketone at C-10. To this end, sequential treatment of **19** with lithium bis(trimethylsilyl)amide and phenylselenenyl bromide accomplishes the formation of selenide **20** in 83% yield (see Scheme 5). Selenium-based reagents are extremely versatile in organic synthesis,¹³ and, in this context, the phenylselenide grouping in **20** serves as a latent carbonyl group; a seleno-Pummerer rearrangement accomplishes the conversion of an organoselenide to a ketone.¹⁴ Thus, oxidation of the selenium atom in **20** with hydrogen peroxide furnishes selenoxide **21**. Acylation of the selenoxide oxygen with acetic anhy-



Scheme 5. Synthesis of (±)-periplanone B [(±)-1].



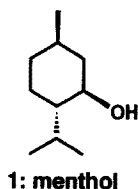
dride, followed by treatment with basic methanol, furnishes, through the cascade of reactions illustrated in Scheme 5, α -diketone **22** in an overall yield of 60% from **20**. When **22** is exposed to dimethylsulfonium methylide, racemic periplanone B [(±)-**1**] is formed as the major product in a yield of 62%.

21.4 Conclusion

It is incumbent upon us to emphasize that the most productive and impressive transformations in Schreiber's periplanone B synthesis are initiated simply by light and heat. The model study and the total synthesis discussed in this chapter reaffirm the utility of the anionic oxy-Cope ring-expansion process for the construction of 5-cyclodecen-1-one frameworks. The carbon-carbon double bond and keto functions of such frameworks provide convenient opportunities for further functionalization, thereby allowing the elaboration of a variety of complex cyclodecanoid systems. In only two steps, bicyclic β,γ -unsaturated ketone **15a**, the product of a completely regioselective [2+2] photocycloaddition reaction between simple starting materials, is converted into cyclodecenone **13**. The position of the carbon-carbon double bond in the cyclobutene **13** permits a thermally allowed conrotatory electrocyclic ring opening¹⁵ to give the conjugated 1,3-diene moiety. Of course, this conjugated diene unit is not only expressed in the natural product, but it also imposes a marked influence on the conformation of the ten-membered ring in which it is contained. As we have seen, this feature was masterfully exploited by Schreiber and Santini to control the stereochemical course of a crucial oxidation step. We have now witnessed two independent and elegant total syntheses^{8,9} of periplanone B, the potent sex pheromone of the American cockroach, and both illustrate the preparative value of synthetic organic chemistry. The utilization of synthetic periplanone B for the control of the population of the American cockroach has been explored.

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Takasago (1984)

Menthol

22.1 Introduction

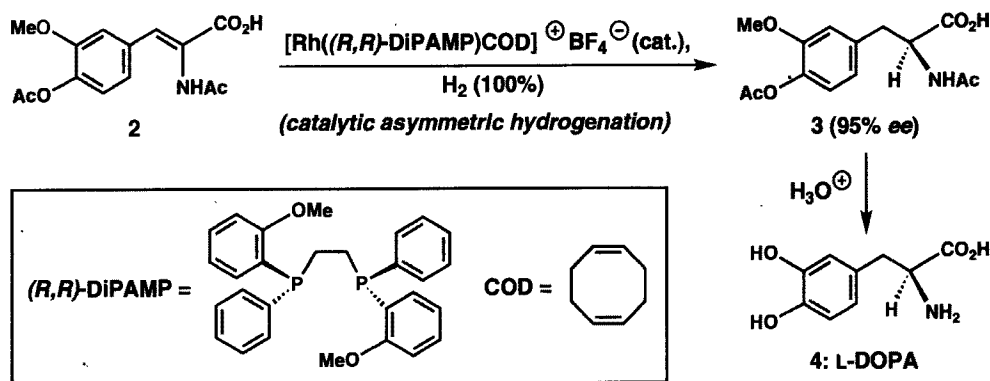
Menthol (**1**), a major constituent of peppermint and other mint oils, is a widely utilized terpene, finding use in confectionery, perfumery, liqueurs, cough drops, cigarettes, toothpaste, and nasal inhalers. In organic synthesis, this naturally occurring substance is a convenient source of chirality, serving as a chiral auxiliary for several asymmetric reactions.¹ Menthol can also be used to esterify racemic carboxylic acids;² after separation of the resulting diastereomeric mixture of menthol esters, a simple ester hydrolysis step can provide both enantiomers of the carboxylic acid in enantiomerically pure form. In another important process, reaction of diastereomerically pure sulfinate esters of menthol with organometallic reagents results in the formation of optically active sulfoxides.³ Introduced by Andersen in 1962, this method is still among the most popular for the preparation of optically active sulfoxides. With so many uses, menthol is a very popular commercial item; approximately 3500 tons of menthol are produced per year.

Perhaps the most successful industrial process for the synthesis of menthol is employed by the Takasago Corporation in Japan.⁴ The elegant *Takasago Process* uses a most effective catalytic asymmetric reaction – the (*S*)-BINAP-Rh(I)-catalyzed asymmetric isomerization of an allylic amine to an enamine – and furnishes approximately 30% of the annual world supply of menthol. The asymmetric isomerization of an allylic amine is one of a large and growing number of catalytic asymmetric processes. Collectively, these catalytic asymmetric reactions have dramatically increased the power and scope of organic synthesis. Indeed, the discovery that certain chiral transition metal catalysts can dictate the stereo-

chemical course of fundamental reactions such as hydrogenations, isomerizations, epoxidations, dihydroxylations, cyclopropanations, and aziridinations of alkenes, carbonyl reductions, carbonyl additions, aldol condensations, and pericyclic reactions has revolutionized organic synthesis (see Schemes A1–A18 in the Appendix to this chapter for representative examples and references).^{5–55}

In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral. In recent years, synthetic chemists have developed numerous catalytic asymmetric reaction processes that transform prochiral substrates into chiral products with impressive margins of enantioselectivity, feats that were once the exclusive domain of enzymes.⁵⁶ These developments have had an enormous impact on academic and industrial organic synthesis. In the pharmaceutical industry, where there is a great emphasis on the production of enantiomerically pure compounds, effective catalytic asymmetric reactions are particularly valuable because one molecule of an enantiomerically pure catalyst can, in principle, direct the stereoselective formation of millions of chiral product molecules. Such reactions are thus highly productive and economical, and, when applicable, they make the wasteful practice of racemate resolution obsolete.

An early success story in the field of catalytic asymmetric synthesis is the *Monsanto Process* for the commercial synthesis of L-DOPA (**4**) (see Scheme 1), a rare amino acid that is effective in the treatment of Parkinson's disease.⁵⁷ The *Monsanto Process*, the first commercialized catalytic asymmetric synthesis employing a chiral transition metal complex, was introduced by W.S. Knowles and coworkers and has been in operation since 1974. This large-scale process for the synthesis of L-DOPA (**4**) is based on catalytic asymmetric hydrogenation, and its development can be

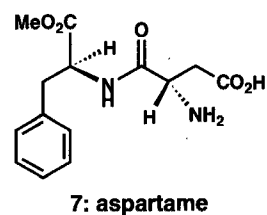
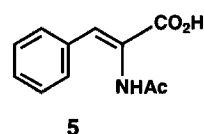
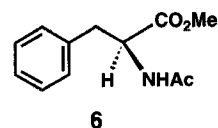


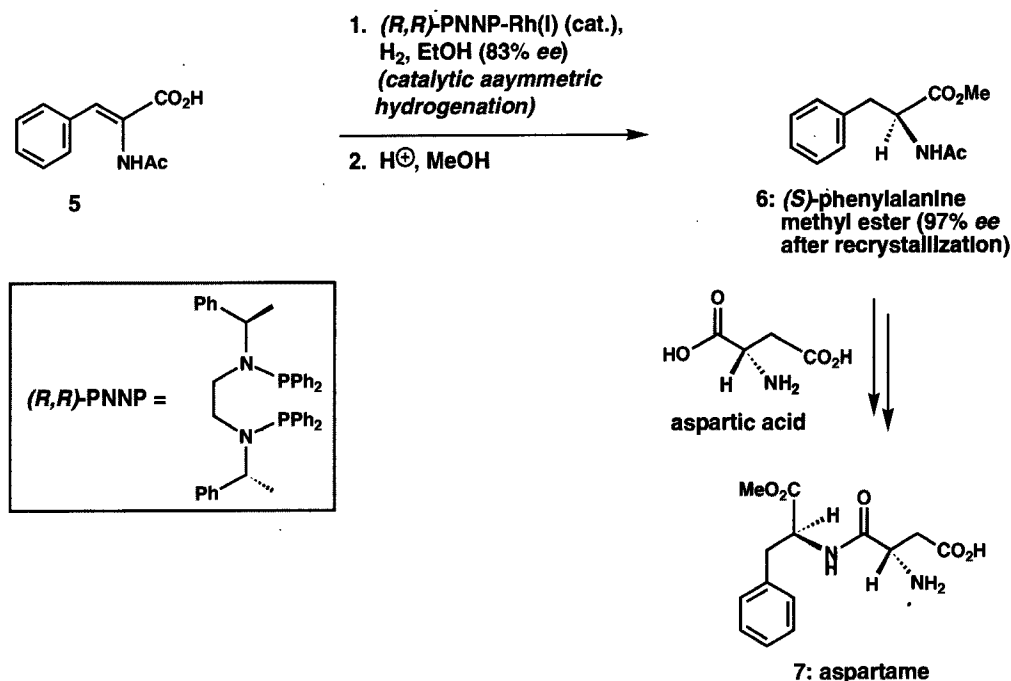
Scheme 1: The Monsanto synthesis of L-DOPA (**4**) using catalytic asymmetric hydrogenation.

traced to Wilkinson's pioneering discovery of the homogeneous hydrogenation catalyst, tris(triphenylphosphine)rhodium chloride $[(\text{Ph}_3\text{P})_3\text{RhCl}]$, in 1966.⁵⁸ Wilkinson's catalyst is a soluble transition metal complex that catalyzes the hydrogenation of unhindered olefins with rates that compare favorably to those obtained with the familiar heterogeneous catalysts. Soon after this important discovery, several groups, including the Monsanto group, demonstrated that replacement of the achiral triphenylphosphine ligands of Wilkinson's catalyst with chiral phosphines afforded optically active hydrogenation catalysts that could effect enantioselective olefin hydrogenations, albeit with rather low enantiomeric excesses. Nonetheless, during the course of this work, Knowles and coworkers at Monsanto discovered that a cationic rhodium complex bearing DiPAMP (see Scheme 1), a chelating diphosphine with two chiral phosphorus atoms, can catalyze highly enantioselective hydrogenations of enamides such as **2**. Enamides are, in fact, exceptional substrates for catalytic asymmetric hydrogenation. In the key step of the synthesis of L-DOPA by Monsanto, enamide **2** is hydrogenated in the presence of a catalytic amount of $[\text{Rh}((R,R)\text{-DiPAMP})\text{COD}]^+\text{BF}_4^-$ affording protected amino acid **3** in quantitative yield and in 95% *ee*. A simple acid-catalyzed hydrolysis step completes the synthesis of L-DOPA (**4**).

The spectacular success of the commercial L-DOPA synthesis by Monsanto has significantly contributed to the explosive growth of research aimed at the development and application of other catalytic asymmetric reactions in ensuing years. Since the introduction of the *Monsanto Process* in the early seventies, several other commercial syntheses based on powerful catalytic asymmetric reactions have emerged as a result of a productive interplay between academic and industrial research. For example, the acetamide of (*S*)-phenylalanine methyl ester (**6**) (see Scheme 2) is available in bulk by a two-step reaction sequence that features a Rh-catalyzed enantioselective hydrogenation of enamide **5**. The key asymmetric hydrogenation step is conducted in ethanol at a substrate:catalyst ratio of 1500:1. Although the enantiomeric excess for the hydrogenation step is only 83%, a simple recrystallization of amino ester **6** raises the enantiomeric purity to 97%. The acetamide of (*S*)-phenylalanine methyl ester (**6**) is a key intermediate in the commercial synthesis of the non-nutritive sweetener aspartame (**7**) by Anic and Enichem.^{4b,5r}

The emergence of the powerful Sharpless asymmetric epoxidation (SAE) reaction in the 1980s has stimulated major advances in both academic and industrial organic synthesis.¹⁴ Through the action of an enantiomerically pure titanium/tartrate complex, a myriad of achiral and chiral allylic alcohols can be epoxidized with exceptional stereoselectivities (see Chapter 19 for a more detailed discussion). Interest in the SAE as a tool for industrial organic synthesis grew substantially after Sharpless *et al.* discovered that the asymmetric epoxidation process can be conducted with catalytic amounts of the enantiomerically pure titanium/tartrate complex simply by adding molecular sieves to the epoxidation reaction mix-

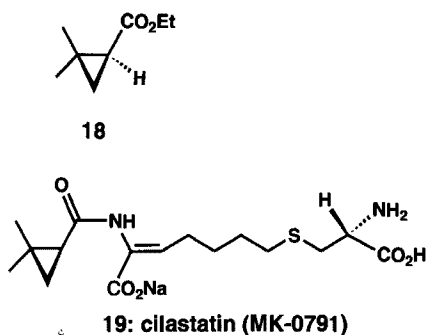


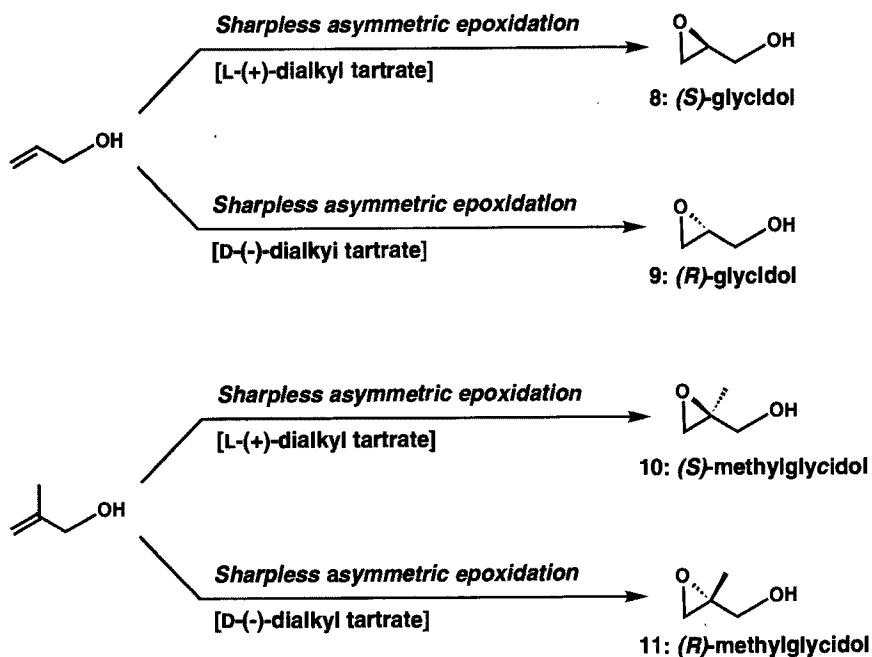


Scheme 2. Anic and Enichem's commercial synthesis of aspartame (**7**) using catalytic asymmetric hydrogenation.

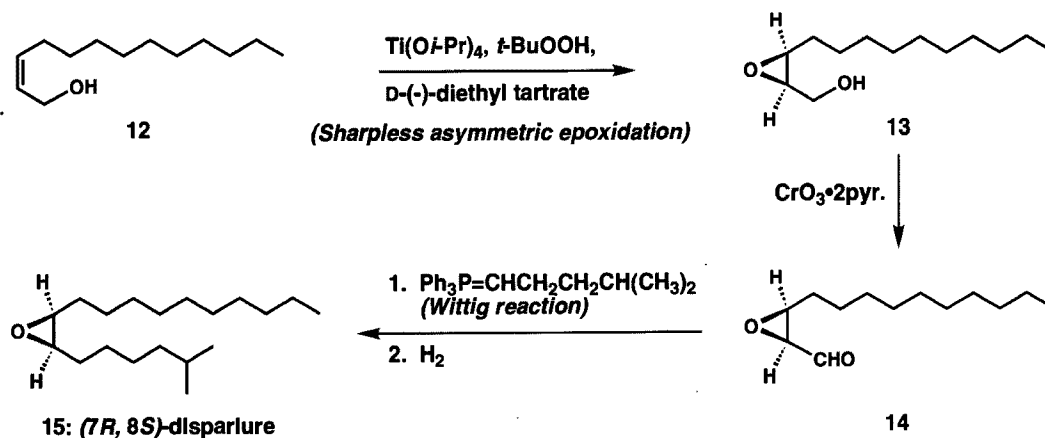
ture.⁵⁹ Using this practical and reproducible catalytic variant, the ARCO chemical company developed an industrial process for ton-scale productions of *(S)*- and *(R)*-glycidol (see **8** and **9**, Scheme 3) and *(S)*- and *(R)*-methylglycidol (see **10** and **11**, Scheme 3). These low molecular weight epoxy alcohols are versatile building blocks for the syntheses of a number of chiral molecules.⁶⁰ It has been reported^{4b} that the commercial production of optically active glycidols in this manner is more viable financially than the competitive route to glycidols based on the porcine pancreatic lipase catalyzed hydrolysis of glycidyl butyrate.⁶¹ In another successful industrial application of the SAE, the J.T. Baker Company adapted Sharpless's synthesis of *(7R,8S)*-disparlure (**15**)⁶² (see **12** → **13** → **14** → **15**, Scheme 4), the pheromone of the gypsy moth, to the commercial production of this valuable compound.

The catalytic asymmetric cyclopropanation of an alkene, a reaction which was studied as early as 1966 by Nozaki and Noyori,⁶³ is used in a commercial synthesis of ethyl (+)-(1*S*)-2,2-dimethylcyclopropanecarboxylate (**18**) by the Sumitomo Chemical Company (see Scheme 5).⁶⁴ In Aratani's *Sumitomo Process*, ethyl diazoacetate is decomposed in the presence of isobutene (**16**) and a catalytic amount of the dimeric chiral copper complex **17**. Compound **18**, produced in 92% ee, is a key intermediate in Merck's commercial synthesis of cilastatin (**19**). The latter compound is a reversible

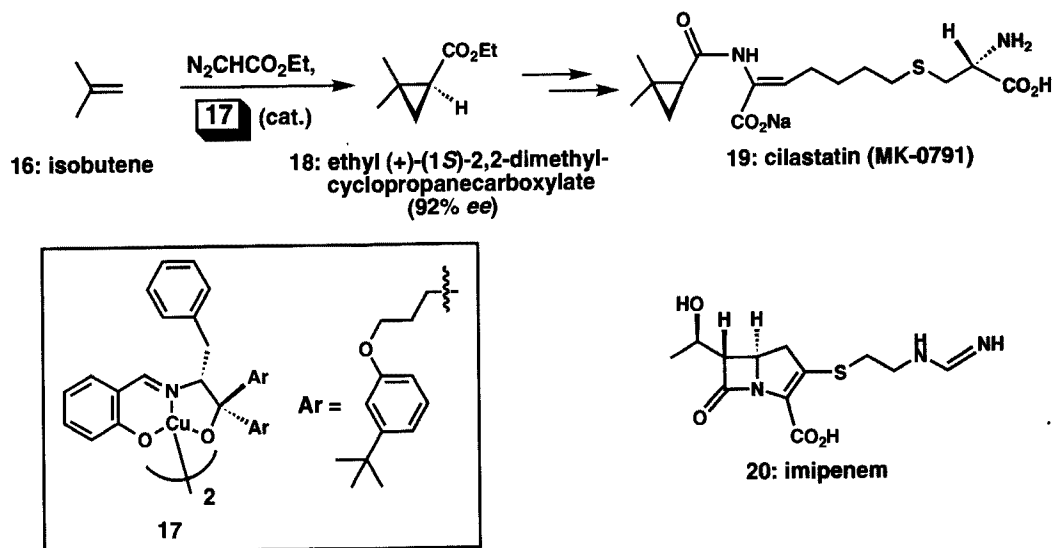




Scheme 3. The ARCO Chemical Company's commercial synthesis of the glycidols using the Sharpless asymmetric epoxidation reaction.



Scheme 4. The Sharpless asymmetric epoxidation in the J. T. Baker Company's commercial synthesis of (7R,8S)-disparlure (15).

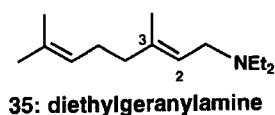


Scheme 5. The Sumitomo Chemical Company's catalytic asymmetric synthesis of ethyl (+)-(1*S*)-2,2-dimethylcyclopropanecarboxylate (**18**), an intermediate in Merck's commercial synthesis of cilastatin (**19**).

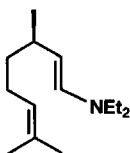
inhibitor of the renal enzyme dehydropeptidase I and serves as an *in vivo* stabilizer of the β -lactam antibiotic, imipenem (**20**, Scheme 5); a combination of cilastatin (**19**) and imipenem (**20**) is a successful pharmaceutical marketed by Merck.

At the present time, the world's largest application of homogeneous asymmetric catalysis is the *Takasago Process* for the commercial synthesis of (–)-menthol (**1**) (*vide infra*).^{4,5d} In the key step of this synthesis, a rhodium(I) catalyst containing the enantiomerically pure ligand (*S*)-BINAP effects the enantioselective isomerization of diethylgeranylamine (**35**) to the isomeric enamine **44** (see **35** → **44**, Scheme 12). The chemical yield for this asymmetry-inducing step is essentially quantitative and the enantiomeric excess of the enamine product is $\geq 98\%$. The remainder of this chapter will address the BINAP-Rh(I)-catalyzed asymmetric isomerization of allylic amines to enamines in greater detail, including the elegant asymmetric synthesis of (–)-menthol by the Takasago Corporation.

The isomerization of an allylic amine to an enamine by means of a formal 1,3-hydrogen shift constitutes a relatively small structural change. However, this transformation could be extremely valuable if it could be rendered stereoselective. In important early studies, Otsuka and Tani showed that a chiral cobalt catalyst, prepared *in situ* from a Co(II) salt, a chiral phosphine, and diisobutylaluminum hydride (Dibal-H), can bring about the conversion of certain prochiral olefins to chiral, isomeric olefins by double bond migra-



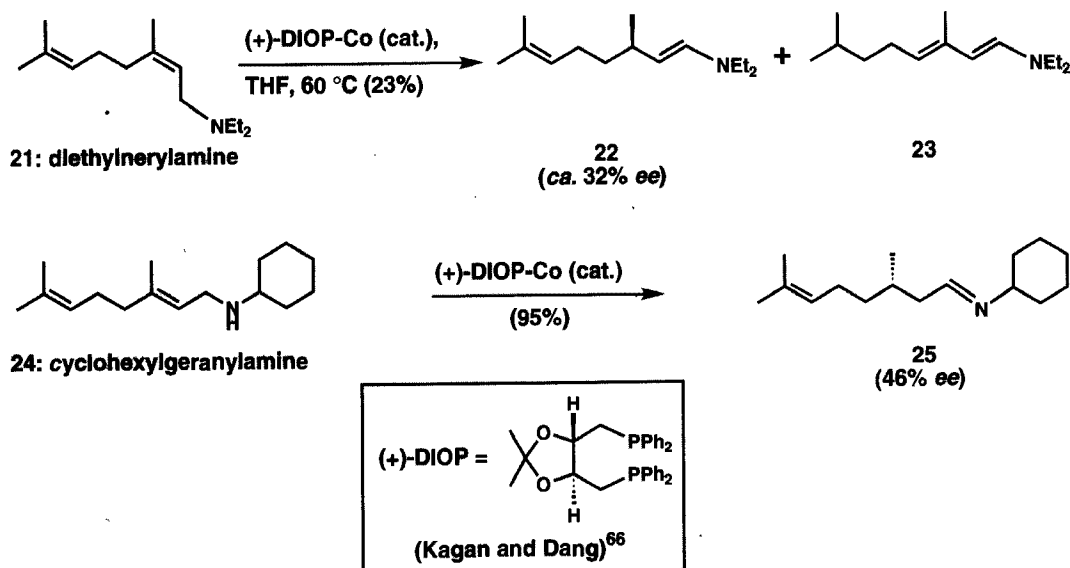
35: diethylgeranylamine



**44: citronellal
(E)-diethylenamine**

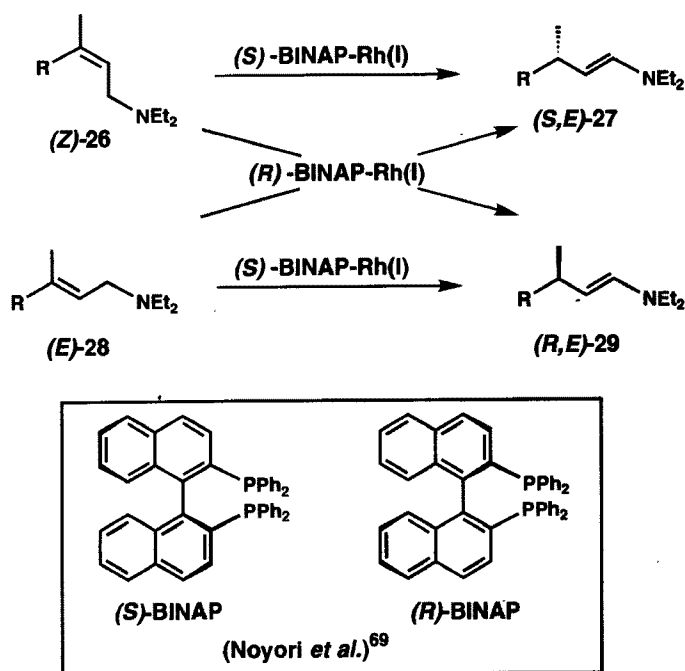
tion.⁶⁵ Using Kagan's historically significant C_2 -symmetric (+)-DIOP ligand (see Scheme 6),⁶⁶ Otsuka *et al.* prepared a (+)-DIOP–Co complex and demonstrated its ability to catalyze an enantioselective isomerization of diethylnerylamine (**21**) to the (*R*)-enamine **22** in *ca.* 32 % *ee* but in only 23 % yield. This transformation is undermined by the production of significant amounts of the undesired conjugated dienamine **23**. Under milder reaction conditions and in the presence of the same (+)-DIOP–Co catalyst, the secondary amine, cyclohexylgeranylamine (**24**) undergoes conversion to the (*S*)-imine **25** with an improved 46 % *ee* and in 95 % yield. Incidentally, when secondary amines are used, the initially formed enamine tautomerizes to the more stable imine. Although the enantioselectivities of these two processes are too low to be of practical use, they represented an important first step in the development of an efficient asymmetric allylic amine isomerization process.

The disclosure, in 1982, that cationic, enantiopure BINAP–Rh(I) complexes can induce highly enantioselective isomerizations of allylic amines in THF or acetone, at or below room temperature, to afford optically active enamines in >95 % yield and >95 % *ee*, thus constituted a major breakthrough.^{67,68} This important discovery emerged from an impressive collaborative effort between chemists representing Osaka University, the Takasago Corporation, the Institute for Molecular Science at Okazaki, Japan, and Nagoya University. BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (Scheme 7), is a fully arylated, chiral diphosphine which was introduced in



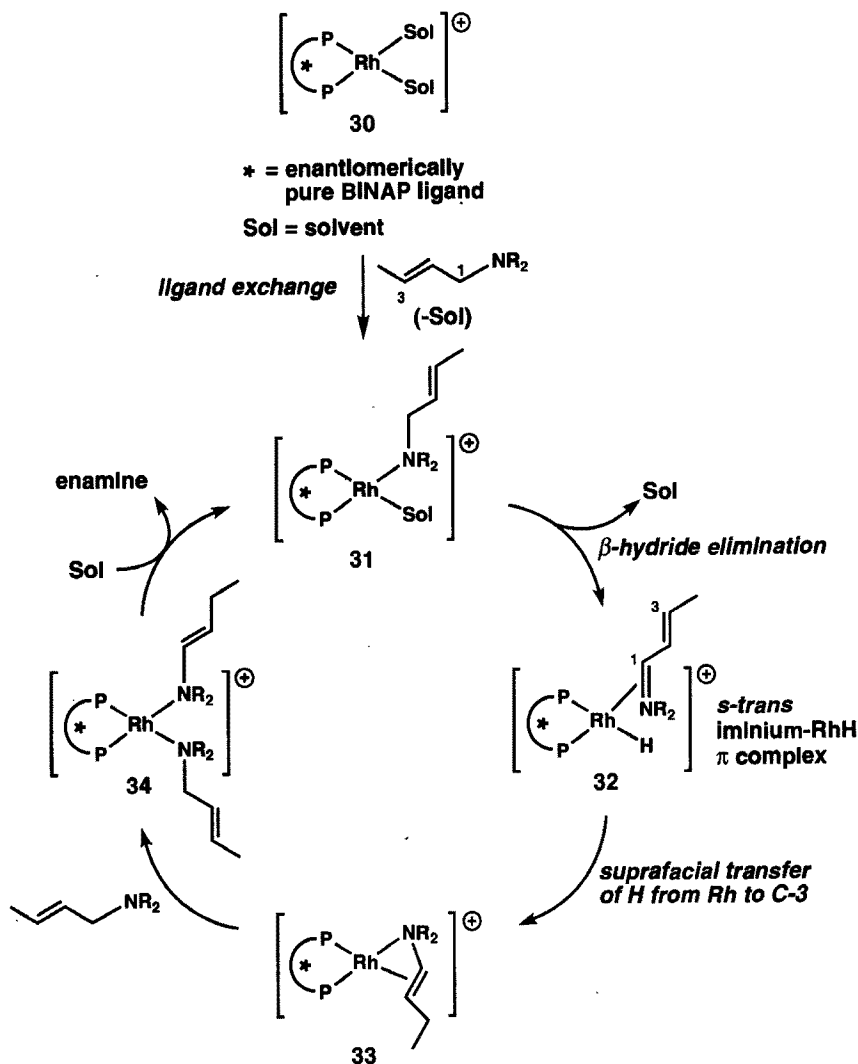
Scheme 6. Otsuka and Tani's (+)-DIOP–Co-catalyzed asymmetric isomerization of diethylnerylamine (**21**) and cyclohexylgeranylamine (**24**).

1980 by Noyori and his colleagues at Nagoya University.⁶⁹ BINAP is a very effective chelating diphosphine chiral ligand for numerous transition metals and is available in both (*R*) and (*S*) enantiomeric forms. In the BINAP–Rh(I)-catalyzed asymmetric isomerization of allylic amines, there is an interesting correlation between the chirality of the BINAP ligand, the configuration of the starting allylic amine (i. e. *E* or *Z*), and the configuration at C-3 in the (*E*)-enamine product (see Scheme 7). For example, in the presence of the (*S*)-BINAP–Rh(I) catalyst, stereochemically pure samples of (*Z*)-allylic amine **26** and (*E*)-allylic amine **28** are isomerized to enantiomeric (*E*)-enamines; with the (*S*)-BINAP–Rh(I) catalyst, (*Z*)-allylic amine **26** is smoothly isomerized to (*S,E*)-enamine **27**, while the stereoisomeric (*E*)-allylic amine **28** is isomerized to (*R,E*)-enamine **29**. If one had access to a particular allylic amine stereoisomer, it would still be possible to obtain, at will, either enamine enantiomer simply by choosing the appropriate BINAP–Rh(I) complex. To obtain excellent enantioselectivities, it is therefore imperative that enantiomerically pure BINAP and configurationally uniform allylic amines be employed. The BINAP–Rh(I)-catalyzed asymmetric isomerization of an allylic amine is a *stereospecific* process, since there is a relationship between starting materials and product stereochemistries.

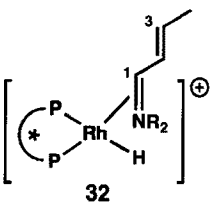
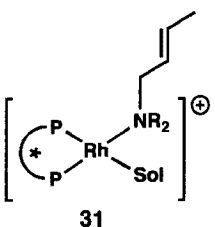
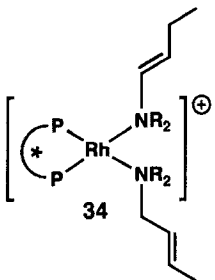
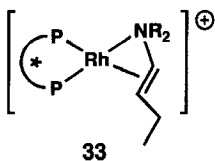


Scheme 7. Stereochemical outcome of BINAP–Rh(I)-catalyzed asymmetric isomerization of allylic amines.

The general picture illustrated in Scheme 7 indicates that an enantiopure BINAP-Rh(I) complex can efficiently recognize the enantiotopic hydrogens at C-1 or the enantiofaces of the $\Delta^{2,3}$ double bond. The mechanism of the BINAP-Rh(I)-catalyzed asymmetric isomerization of an allylic amine is shown in Scheme 8.^{65,68c,70} This reaction commences with a simple ligand exchange between the bis-solvent complex **30** and the allylic amine substrate, generating the nitrogen-coordinated Rh⁺ complex **31**. Loss of a solvent molecule from the square-planar complex **31** initiates a β -hydride elimination reaction to give the transient imi-



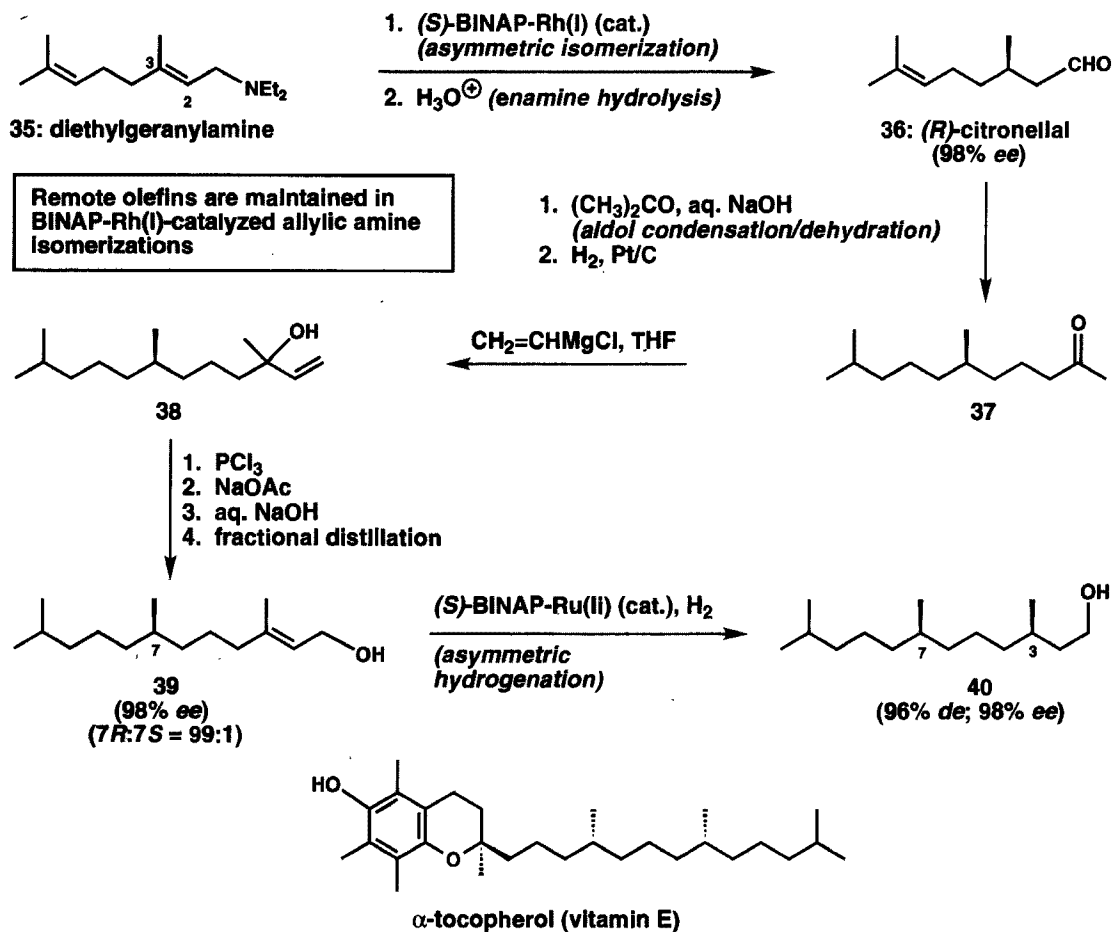
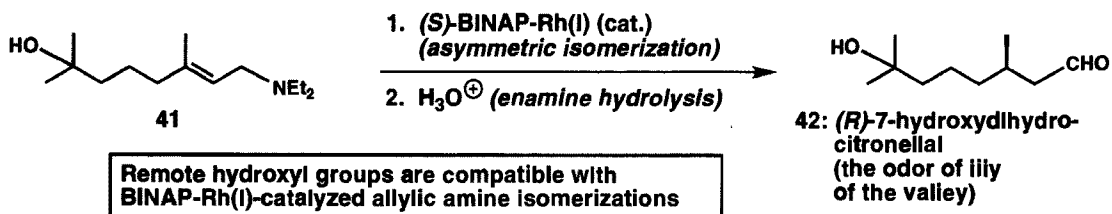
Scheme 8. Catalytic cycle for the BINAP-Rh(I)-catalyzed asymmetric isomerization of allylic amines.



nium-RhH π complex **32**. A suprafacial delivery of the hydrogen atom from Rh to C-3 via an *s-trans* conformer then gives the η^3 -enamine complex **33**. The aza-allyl type complex **33** can be isolated and characterized by NMR spectroscopy, and functions as the chain-carrying species; isolated **33** catalyzes the isomerization of the allylic amine substrate. The replacement of the enamine product in **33** with a new molecule of substrate is the rate-determining step and presumably occurs via the mixed substrate-product complex **34**. Liberation of the enamine product from the mixed-ligand complex **34** produces the reactive 14-electron species **31** and thence iminium-RhH complex **32** through β -hydride elimination, thereby completing the catalytic cycle. The (*S*)-BINAP-Rh catalyst transfers the *pro-S* hydrogen from C-1 to C-3 to give the (3*R,E*)-enamine product, whereas the (*R*)-BINAP-Rh catalyst transfers the *pro-R* C-1 hydrogen to C-3, affording the (3*S,E*)-enamine product. These isomerizations produce only (*E*)-enamines regardless of the configuration of the allylic amine substrate. The chiral, C_2 -symmetric BINAP ligand permits efficient differentiation between the enantiotopic C-1 hydrogens of a prochiral allylic amine.

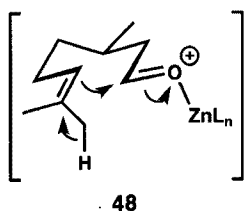
An elegant application of this catalytic enantioselective isomerization process can be found in the synthesis of the side chain of α -tocopherol (vitamin E) by Noyori *et al.* (see Scheme 9).^{10,71} This work actually features two powerful catalytic asymmetric reactions. In the first step, diethylgeranylamine (**35**) is enantioselectively isomerized under the influence of the (*S*)-BINAP-Rh(I) catalyst. Hydrolysis of the resulting (*E*)-enamine product then furnishes (*R*)-citronellal (**36**) in 98% *ee*. It is important to note that only the C2-C3 double bond in **35** is isomerized; a virtue of BINAP-Rh(I)-catalyzed asymmetric isomerizations of allylic amines is that remote double bonds are not affected. The presence of a remote free hydroxyl group is also tolerated (see **41** \rightarrow **42**, Scheme 10). Homologation of (*R*)-citronellal (**36**) (Scheme 9) in the manner shown provides *trans*-trisubstituted allylic alcohol **39** (see **36** \rightarrow **37** \rightarrow **38** \rightarrow **39**, Scheme 9). Hydrogenation of the latter substance in the presence of a catalytic amount of (*S*)-BINAP-Ru(II) creates the second methyl-bearing stereogenic center, affording alcohol **40** stereoselectively (96% *de*; 98% *ee*).

We now turn to the *Takasago Process* for the commercial synthesis of (–)-menthol (**1**),⁴ one of the most successful industrial applications of catalytic asymmetric synthesis. This exquisite synthesis is based on the BINAP-Rh(I)-catalyzed enantioselective isomerization of allylic amines, and has been in operation for the commercial production of (–)-menthol since 1984.

Scheme 9. Synthesis of the side chain of α -tocopherol by Noyori *et al.*

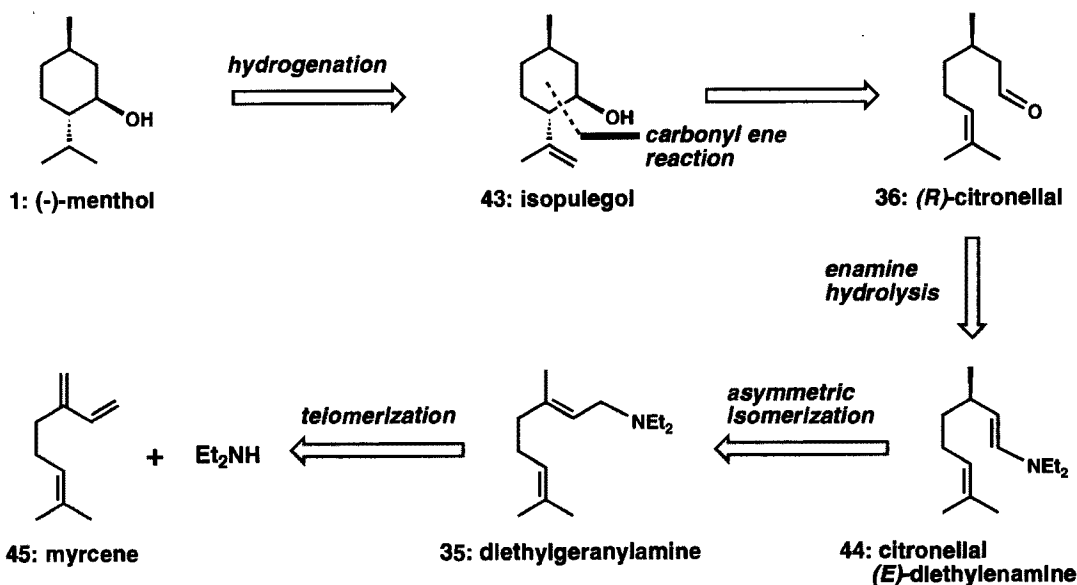
Scheme 10. Catalytic asymmetric synthesis of (R)-7-hydroxydihydrocitronellal (42).

22.2 Retrosynthetic Analysis and Strategy



The cyclohexane framework of (–)-menthol (**1**) is distinguished by three stereogenic centers, two of which are contiguous (see Scheme 11). At the time that the *Takasago Process* was developed, it was well known that (–)-menthol (**1**) could be produced in one step from isopulegol (**43**) through hydrogenation of the carbon–carbon double bond, and that the latter substance could arise from a Lewis acid induced carbonyl ene cyclization of (R)-citronellal (**36**).⁷² Like (–)-menthol (**1**), isopulegol (**43**) and (R)-citronellal (**36**) are both naturally occurring substances. The cycloisomerization of compound **36** to isopulegol (**43**) is particularly productive because it simultaneously creates the requisite six-membered ring and the two contiguous stereogenic centers through an ordered transition state structure (see **48**, Scheme 12).

The synthetic problem is now reduced to the development of a feasible, large-scale preparation of enantiomerically pure (R)-citronellal (**36**), which has a single stereogenic center. One way in which the aldehyde function in **36** could be introduced is through the hydrolysis of a terminal enamine. (R)-Citronellal (**36**) can thus be traced to citronellal (E)-diethylenamine (**44**), the projected product of an enantioselective isomerization of prochiral diethylgera-



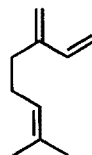
Scheme 11. Retrosynthetic analysis of menthol (**1**).

nylamine (**35**). On the basis of some known chemistry, there was good reason to believe that diethylgeranylamine (**35**), with its *trans*-trisubstituted allylic amine moiety, could be constructed stereoselectively from myrcene (**45**) and diethylamine. Using this elegant plan, the Takasago Corporation developed a highly practical and economically feasible commercial process based on catalytic asymmetric synthesis.

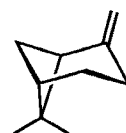
22.3 Total Synthesis

The Takasago synthesis of (–)-menthol commences with the thermal cracking of β-pinene (**46**), a constituent of cheap turpentine, to give myrcene (**45**) (see Scheme 12). Although a conjugated 1,3-diene construct may, at first glance, seem an unlikely precursor to a *trans*-trisubstituted allylic amine, it was known from the work of Takabe and his colleagues⁷³ that *n*-butyllithium can catalyze the reaction of 1,3-dienes with secondary amines to give allylic amines with very good stereoselectivities. In the chemical literature, this type of addition process is frequently referred to as *telomerization*. In the case at hand, myrcene (**45**) and diethylamine join regio- and stereoselectively in the presence of a catalytic amount of *n*-butyllithium to give diethylgeranylamine (**35**). It is presumed that this addition reaction proceeds by way of the *N*-chelated intermediate **47**.

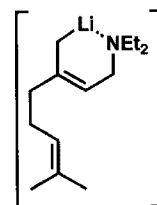
The stage is now set for the crucial catalytic asymmetric isomerization reaction. When diethylgeranylamine (**35**) is treated at 100°C with a small quantity of the catalyst precursor, [Rh((*S*)-BINAP)(COD)]⁺ClO₄[–], citronellal (*R,E*)-diethylenamine (**44**) is formed in quantitative yield and with an enantiomeric excess of >98%. The catalyst precursors, [Rh((*S*)-BINAP)(THF)₂]⁺ClO₄[–] and [Rh((*S*)-BINAP)(MeOH)₂]⁺ClO₄[–] can also be used with equal effectiveness. Process refinements now permit this catalytic asymmetric reaction to be conducted on a 9 ton scale at substrate:catalyst ratios of 8000:1 to 10000:1. The enantiomerically enriched (nearly enantiomerically pure) enamine product can be distilled directly from the reaction mixture at low pressure, and the (*S*)-BINAP–Rh(I) catalyst can be recycled. Using this effective catalytic asymmetric reaction as the central step, the Takasago Corporation produces approximately 1500 tons of (–)-menthol and other terpenic substances annually. From Scheme 7, it should be recognized that citronellal (*R,E*)-diethylenamine (**44**) could just as easily be fashioned from the stereoisomeric (*Z*)-allylic amine [i. e. diethylnerylamine (**21**)] by switching to the enantiomeric (*R*)-BINAP–Rh(I) catalyst. This catalytic asymmetric process is thus not only economical and efficient, but also very flexible. It is also important to note that the remote Δ^{6,7} double bond is impervious to the asymmetric isomerization reaction.



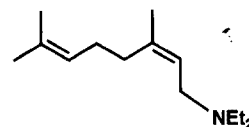
45: myrcene



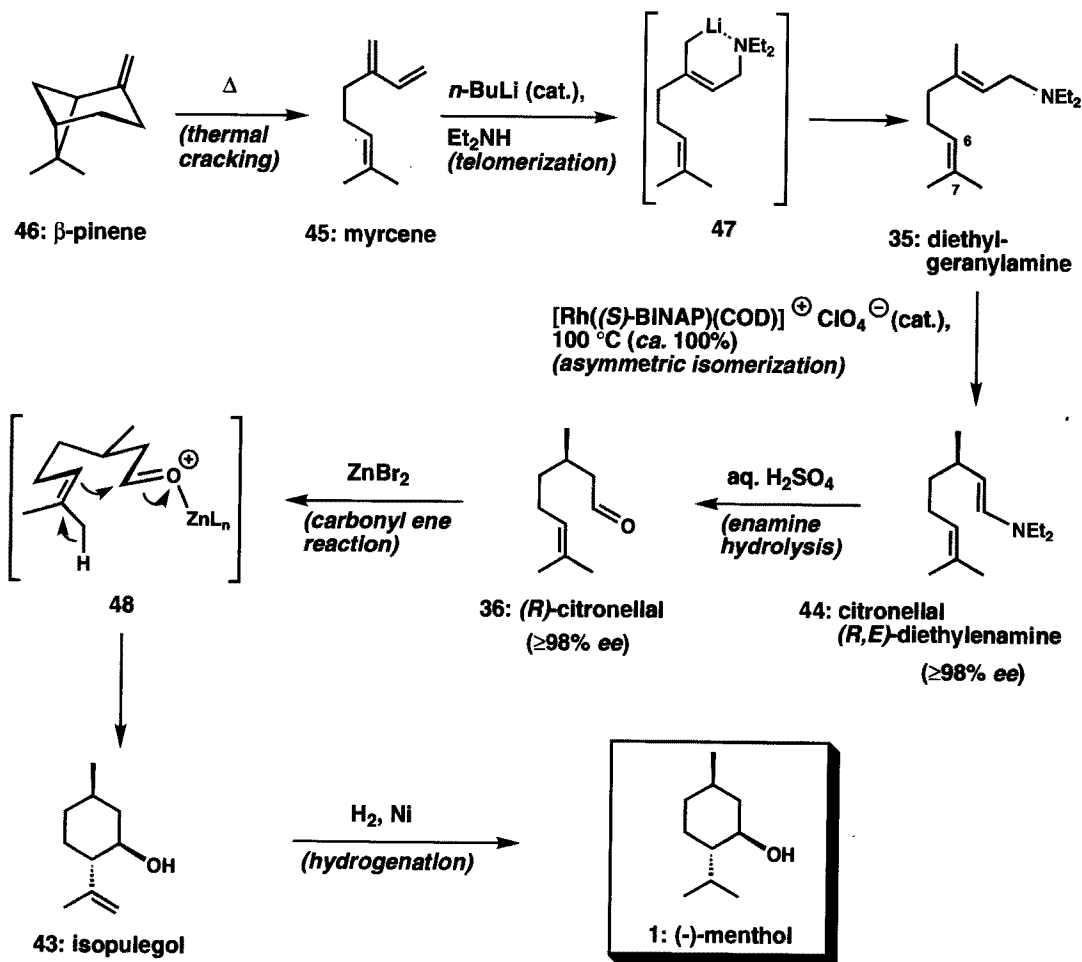
46: β-pinene



47



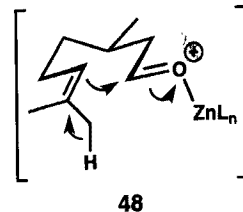
21: diethylnerylamine



Scheme 12. The Takasago process for the asymmetric synthesis of (-)-menthol (1).

With compound **44** in hand, the completion of the synthesis only requires three straightforward operations. As expected, enamine **44** can be converted to (*R*)-citronellal (**36**) by the action of mild aqueous acid. It is of interest that (*R*)-citronellal (**36**), produced in this manner, is of a much higher enantiomeric purity (i.e. 98–99% ee) than the same substance obtained from its natural source! Indeed, the enantiomeric purity of natural (*R*)-citronellal is at best 80%. On the basis of well-established precedent,⁷² it was anticipated all along that the methyl-bearing C-3 stereocenter in citronellal would guide the stereochemical course of a carbonyl ene cyclization⁷⁴ to give the isomeric isopulegol molecule (**43**). Gratifyingly, treatment of (*R*)-citronellal (**36**) with either ZnCl_2 or ZnBr_2 , both active

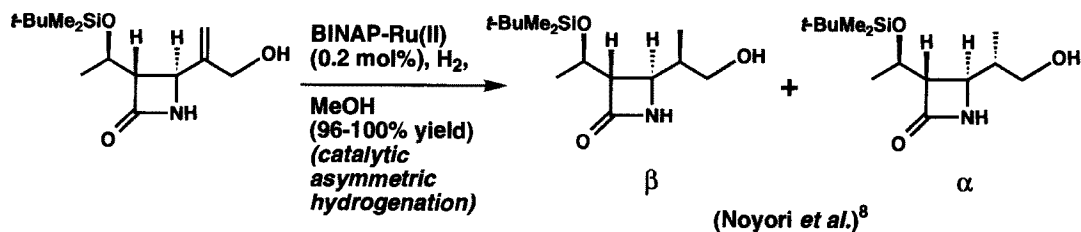
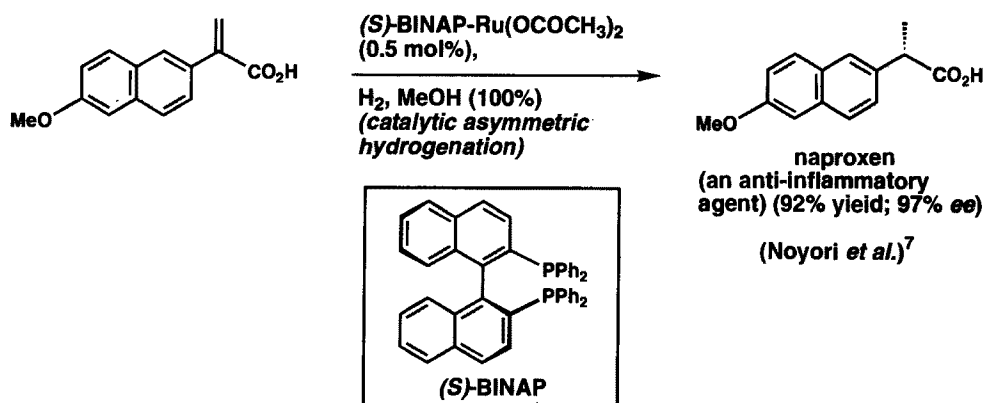
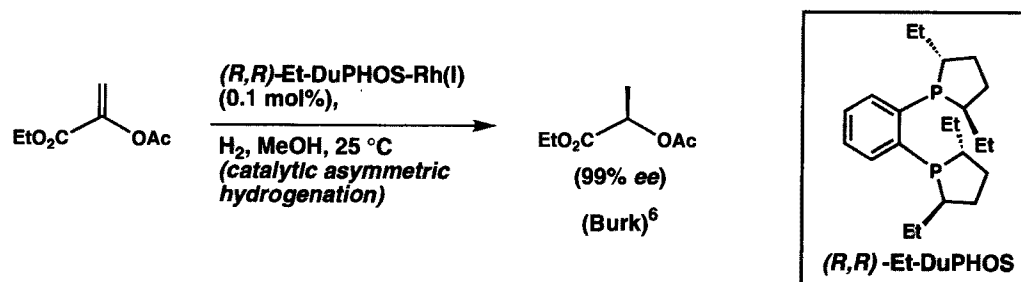
Lewis acids, results in the formation of isopulegol (**43**) with greater than 98 % diastereoselectivity; isopulegol (**43**), wherein all of the ring substituents are equatorially oriented, arises naturally from a chairlike transition state structure in which the C-3 methyl group, the coordinated C-1 aldehyde carbonyl, and the $\Delta^{6,7}$ double bond are all equatorial (see **48**). A low-temperature crystallization raises the chemical and enantiomeric purity of isopulegol (**43**) close to 100 %. Finally, hydrogenation of the double bond in **43** completes the synthesis of (-)-menthol (**1**).



22.4 Conclusion

There can be no doubt that the scope of academic and industrial organic synthesis has been profoundly extended by developments in the field of catalytic asymmetric synthesis. The wide variety of reaction processes that can be catalyzed by soluble transition metal complexes, and the ease with which such complexes can be modified with chiral ligands creates manifold opportunities for the development of new, stereocontrolled reaction processes. In this chapter, some of the most significant recent developments in the field of catalytic asymmetric synthesis were addressed; and the industrial production of (-)-menthol (**1**) by the *Takasago Process*, a prime example of these developments, was described. Advances in this field are among the most exciting and useful in all of organic synthesis. This field is currently considered a major frontier in chemistry, and many new developments are certain to emerge in the future.

22.5 Appendix: Catalytic Asymmetric Reactions, an Overview

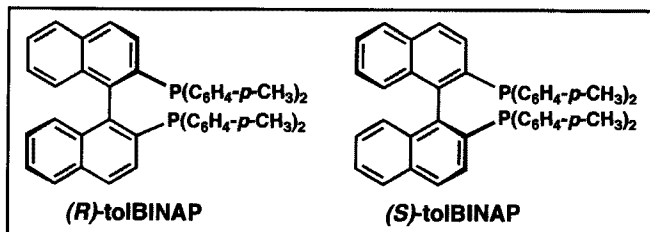


BINAP-Ru(II) = Ru(OCOCH₃)₂[(*R*)-toIBINAP] β:α = 99.9:0.1 (*matched diastereoselectivity*)

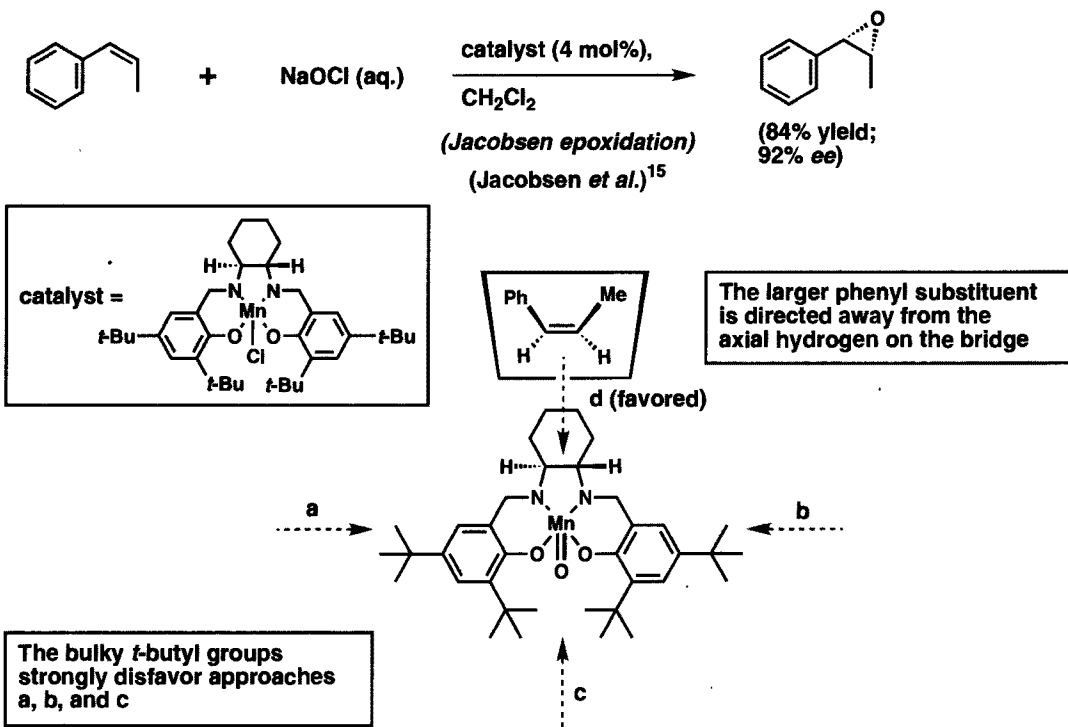
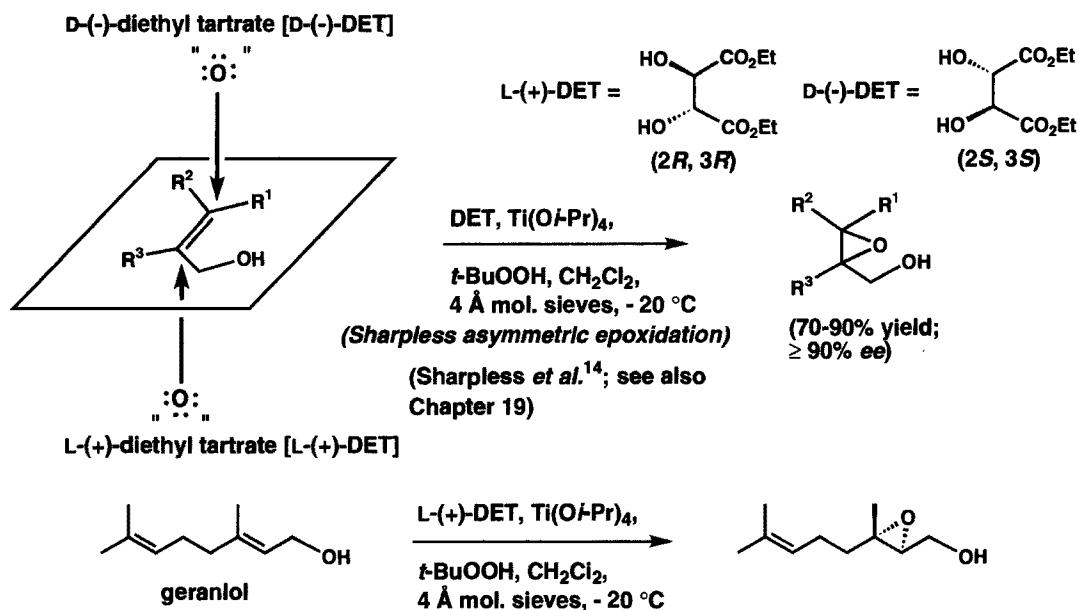
BINAP-Ru(II) = Ru(OCOCH₃)₂[(*S*)-toIBINAP] β:α = 22:78 (*mismatched diastereoselectivity*)

substrate stereofacial preference: β:α = 17:1

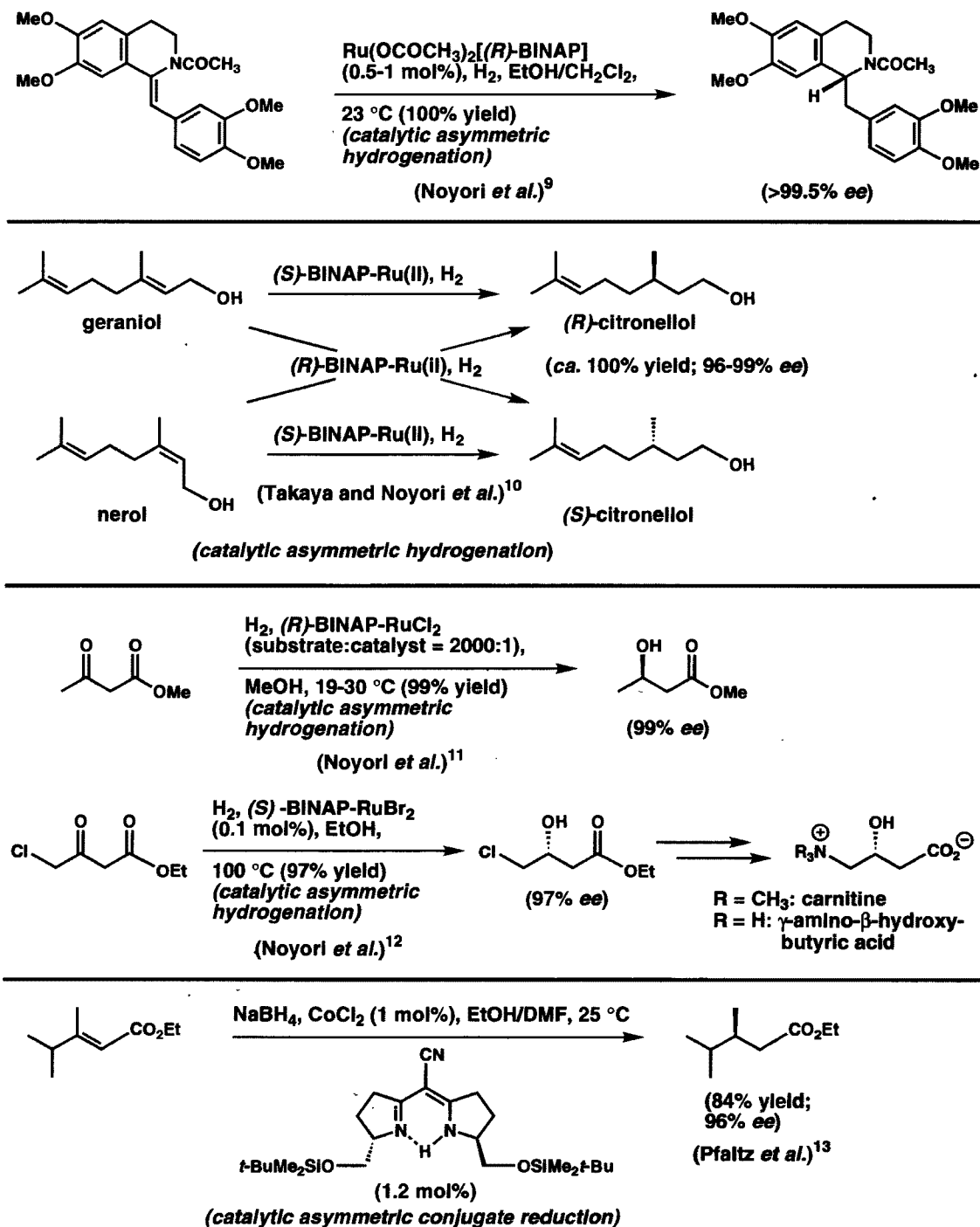
catalyst stereofacial preference: *R*⁺:*S*⁺ = 59:1



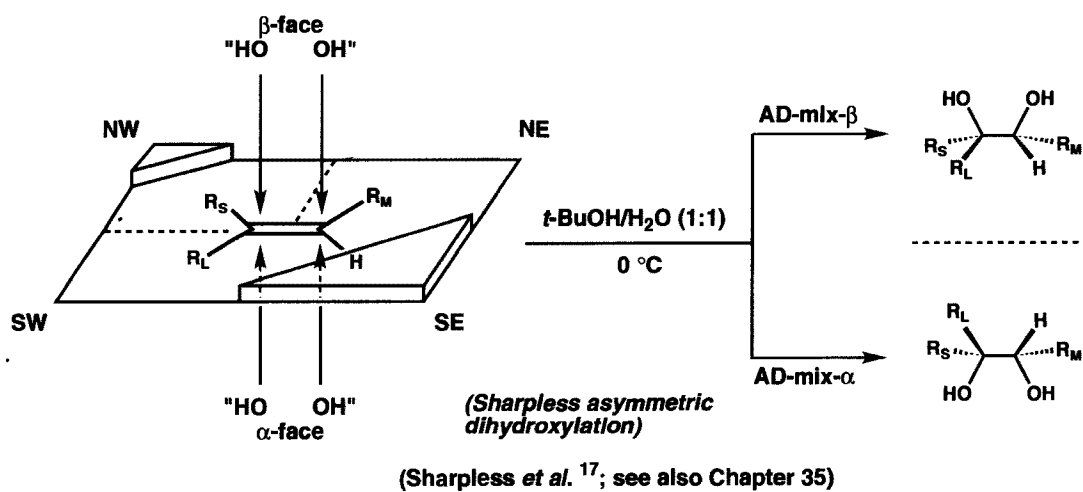
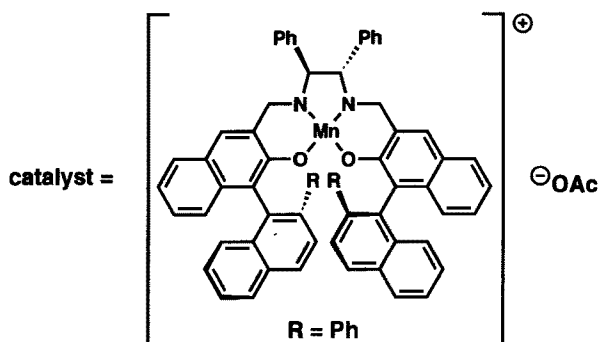
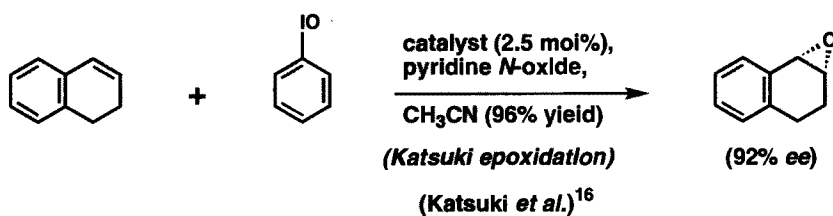
Scheme A1. Representative catalytic asymmetric reactions (references on scheme).



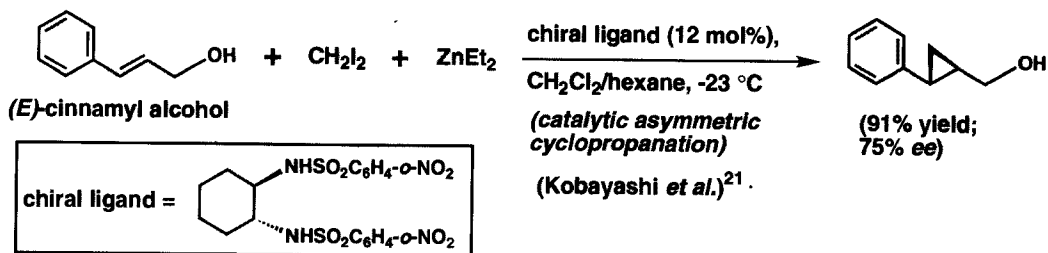
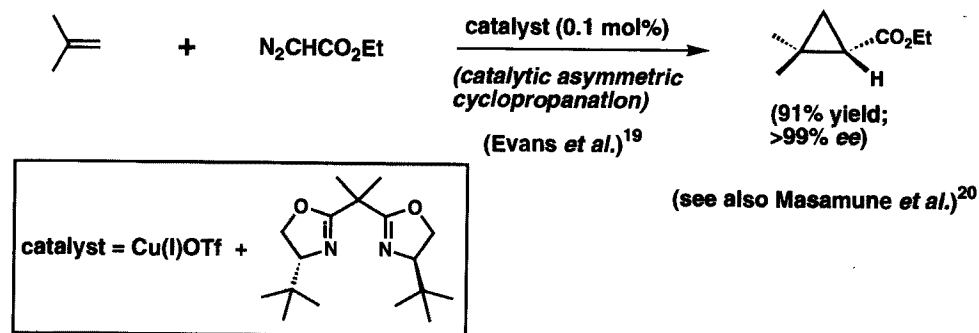
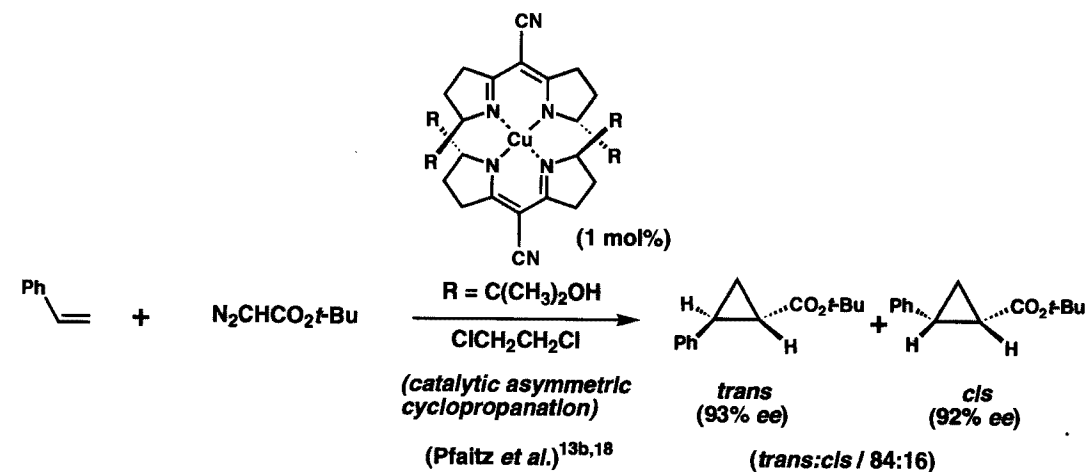
Scheme A2. Representative catalytic asymmetric reactions.



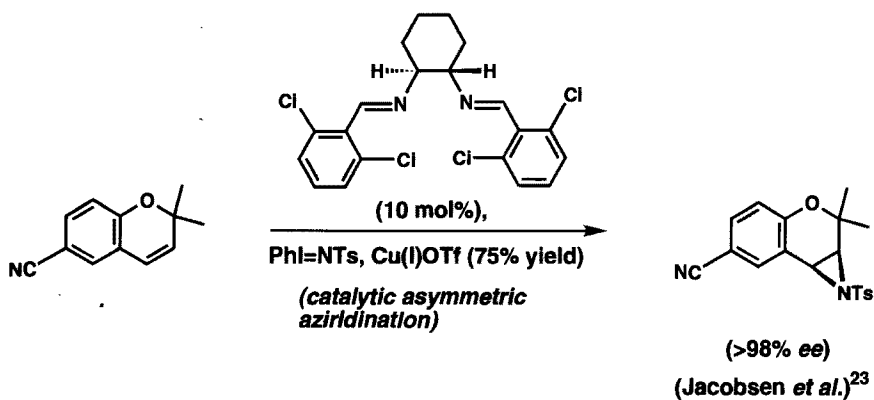
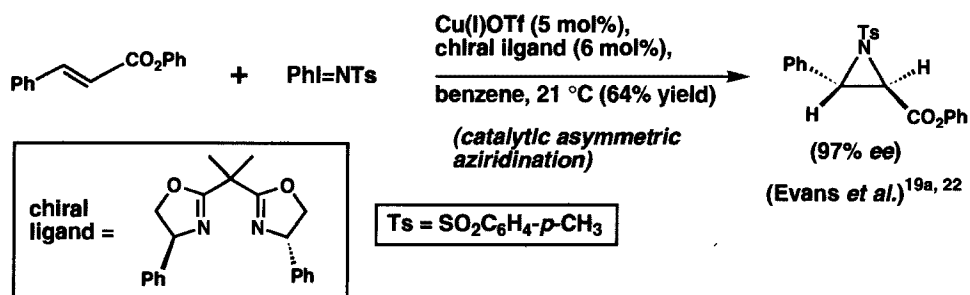
Scheme A3. Representative catalytic asymmetric reactions.

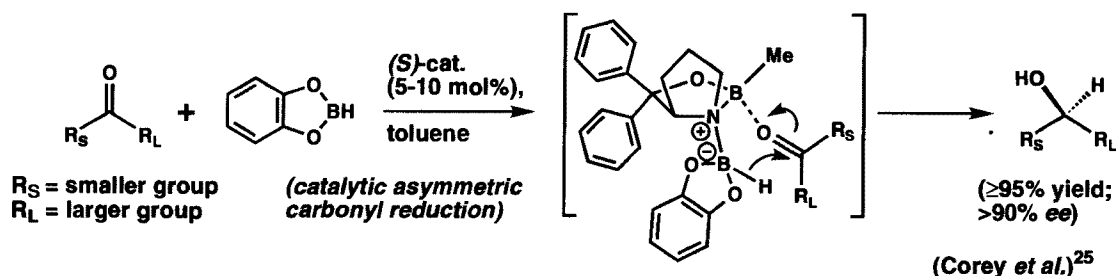
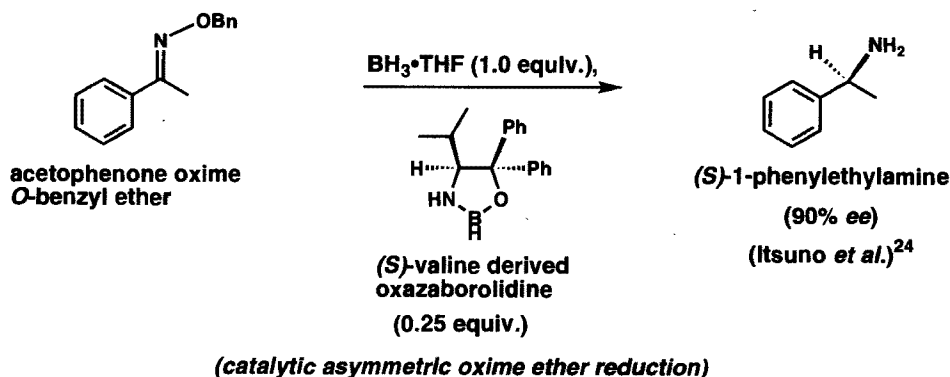


Scheme A4. Representative catalytic asymmetric reactions.

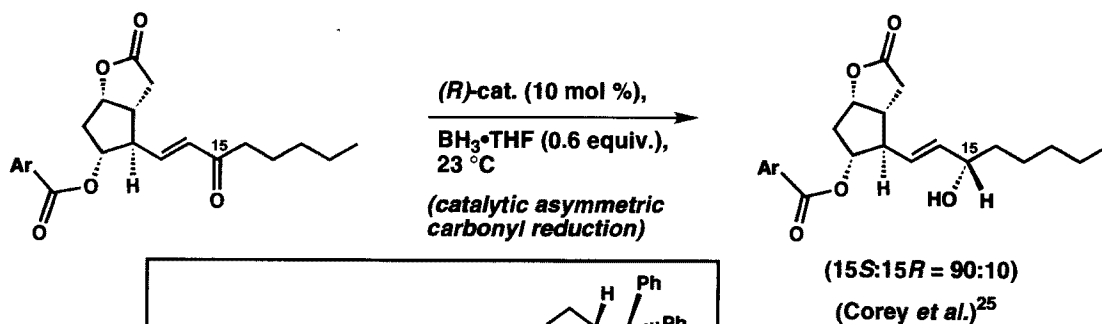
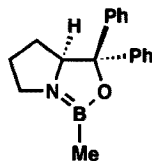


Scheme A5. Representative catalytic asymmetric reactions.

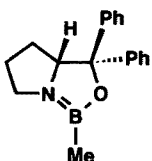
**Scheme A6.** Representative catalytic asymmetric reactions.



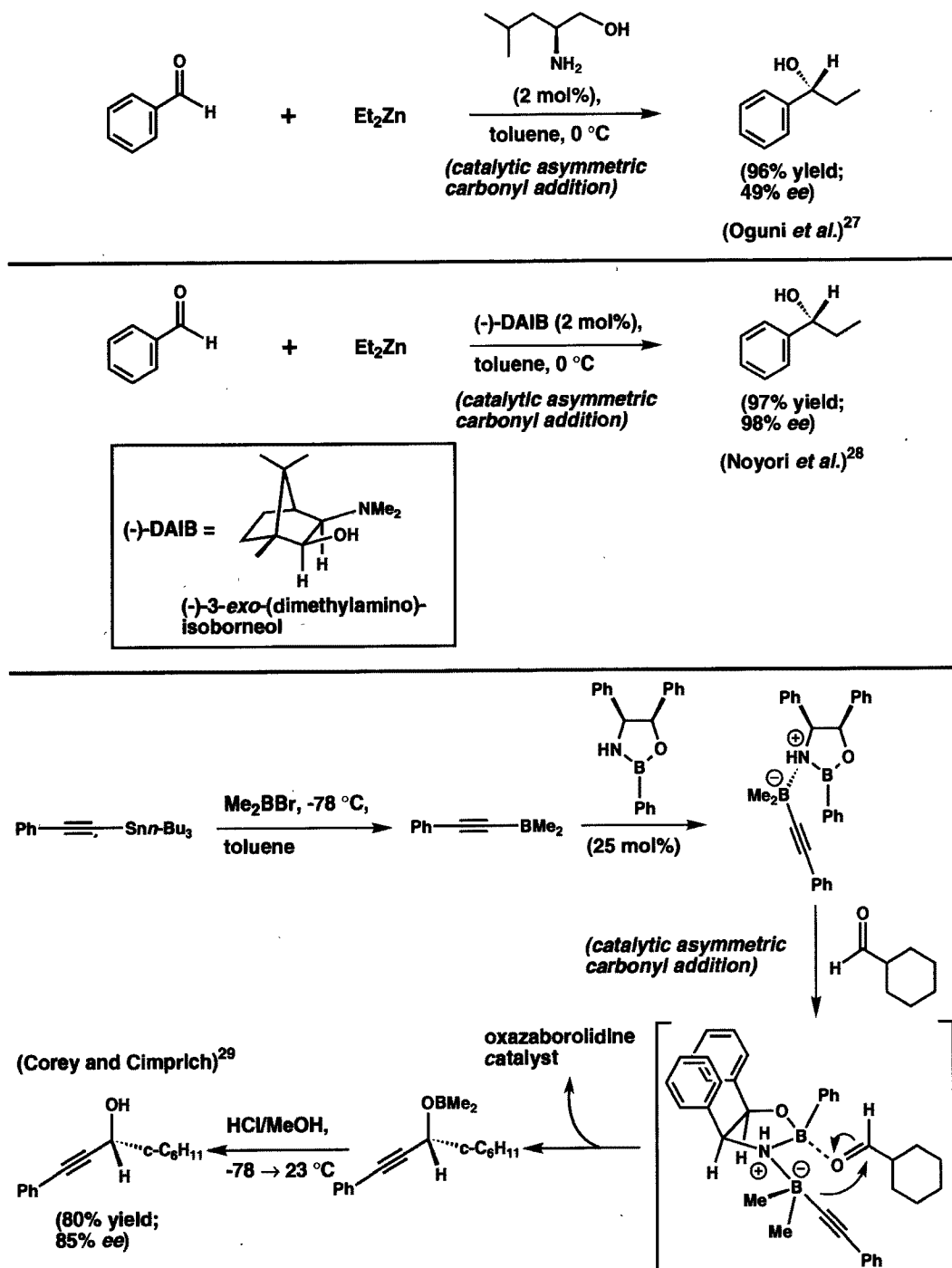
(*S*)-cat. = (*S*)-oxazaborolidine =



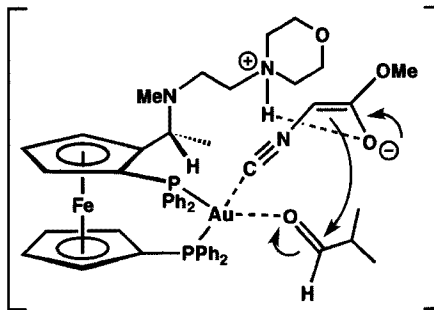
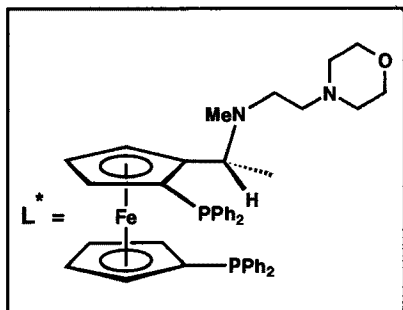
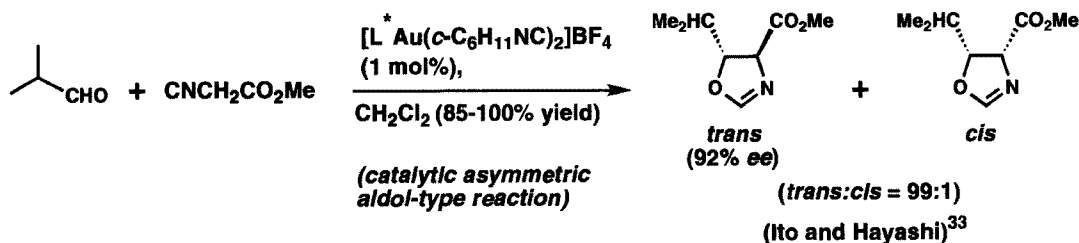
(*R*)-cat. = (*R*)-oxazaborolidine =



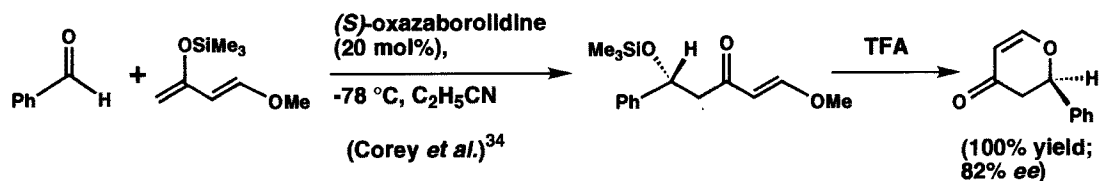
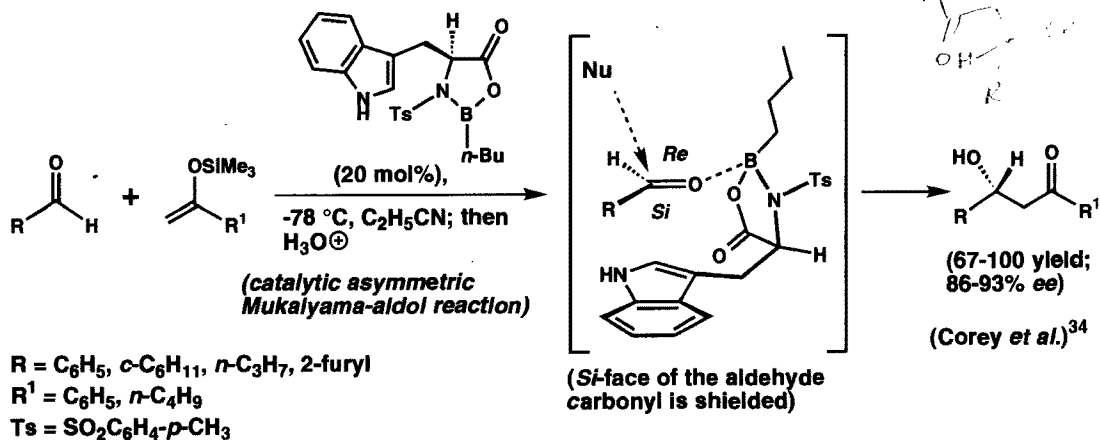
Scheme A7. Representative catalytic asymmetric reactions.



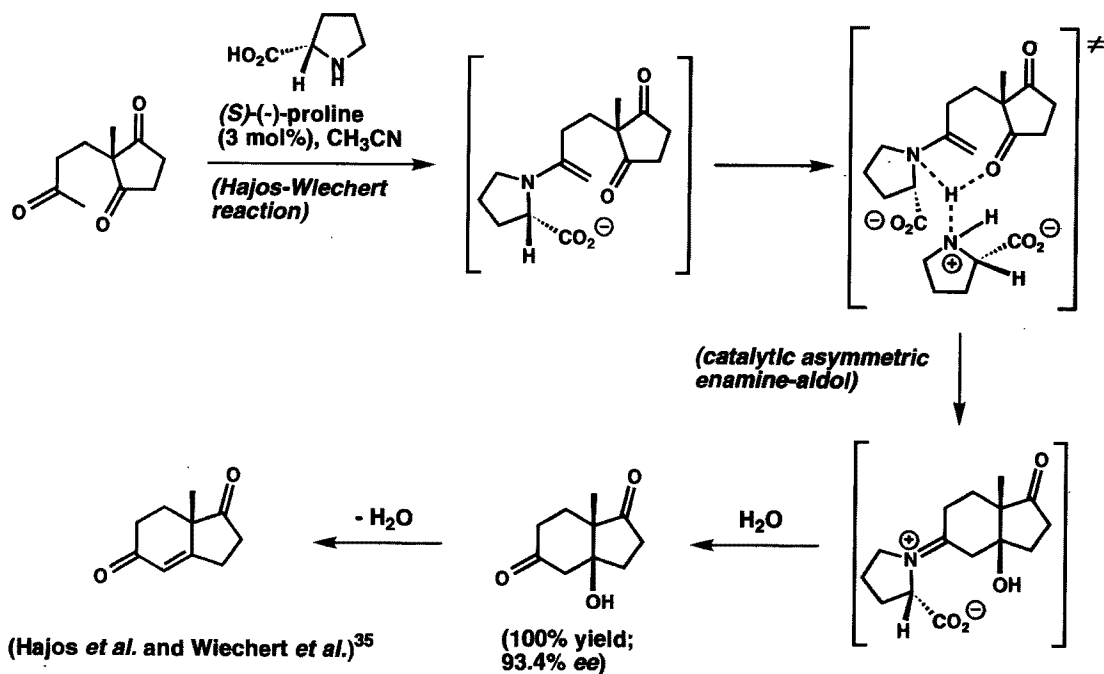
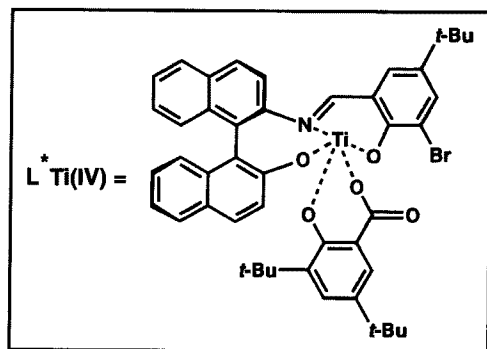
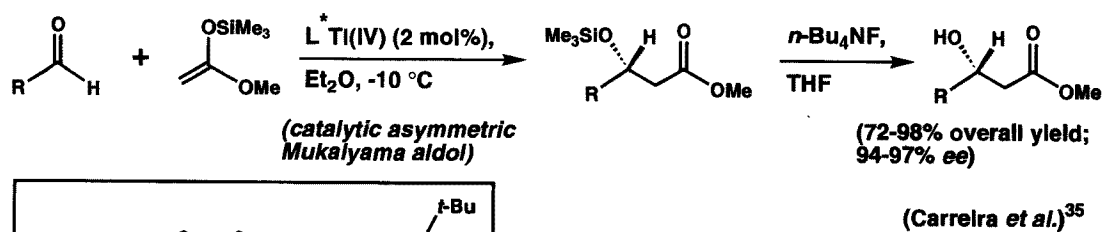
Scheme A8. Representative catalytic asymmetric reactions.



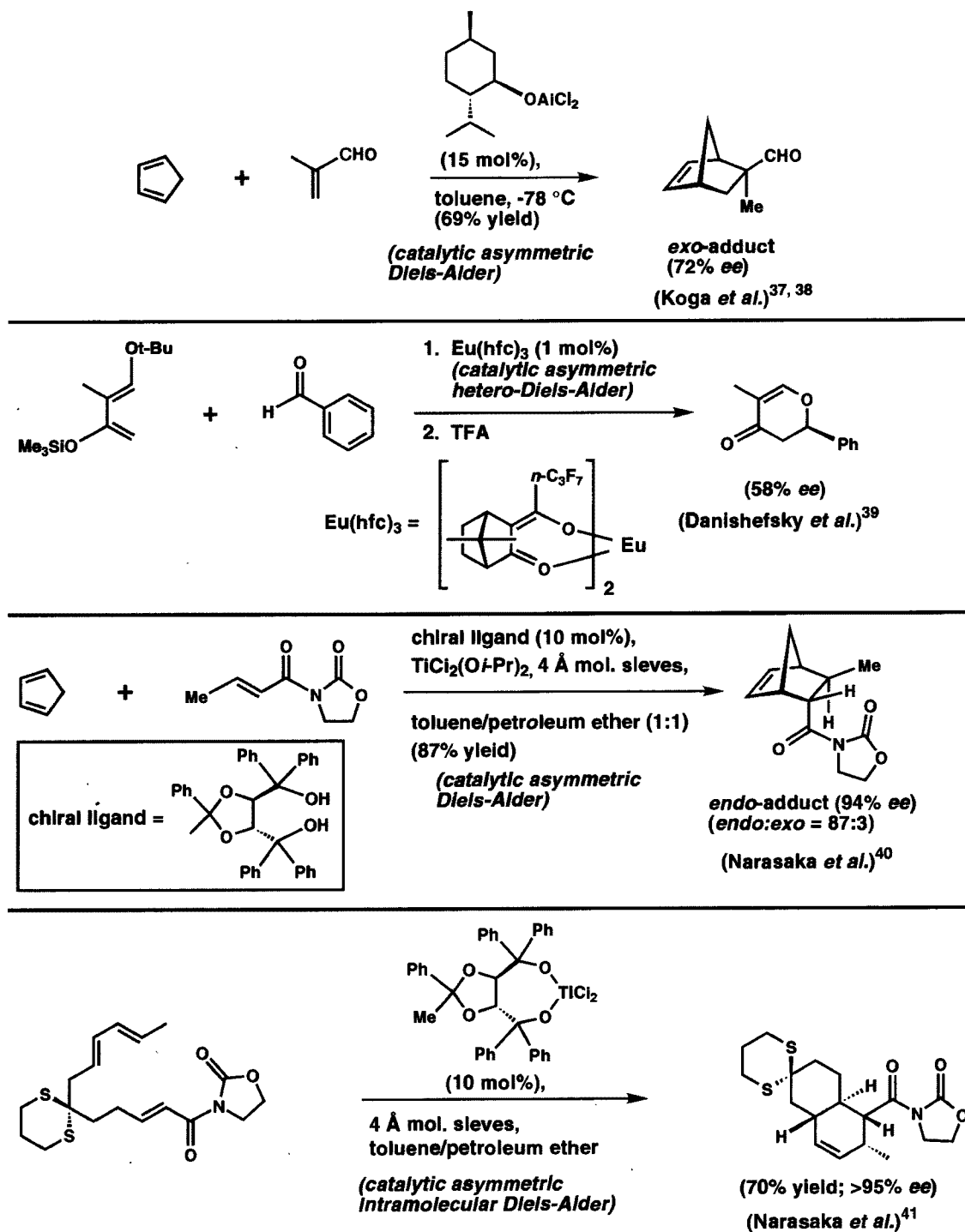
Transition state is stabilized by ammonium ion/enolate ion hydrogen bond



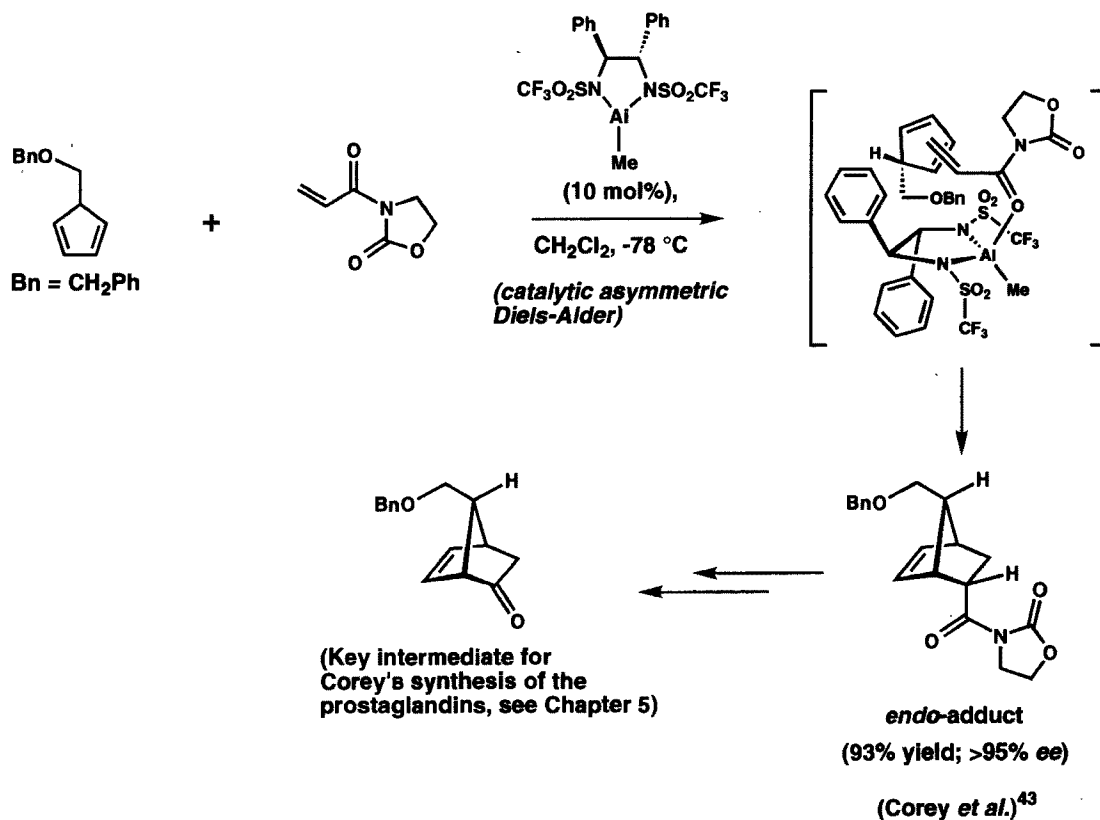
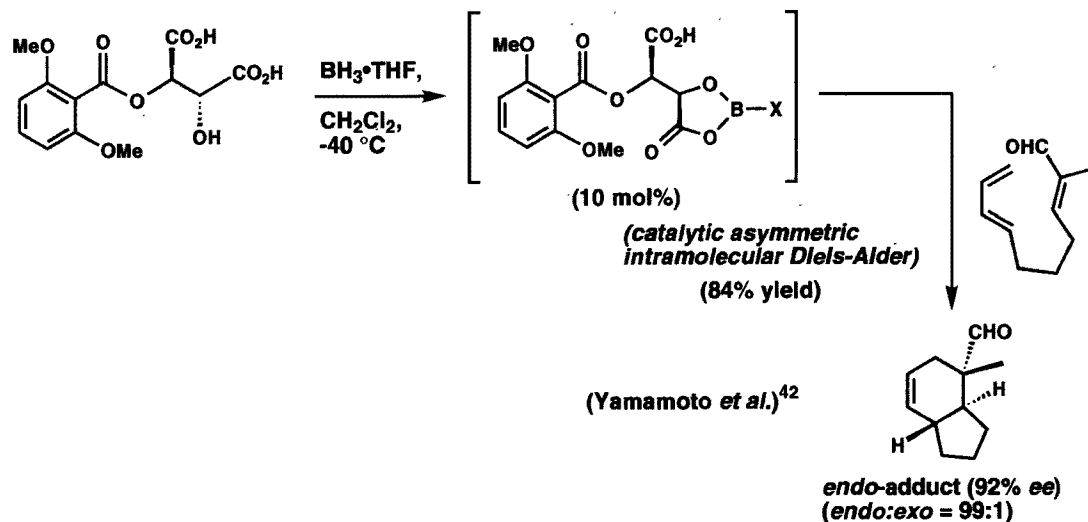
Scheme A10. Representative catalytic asymmetric reactions.



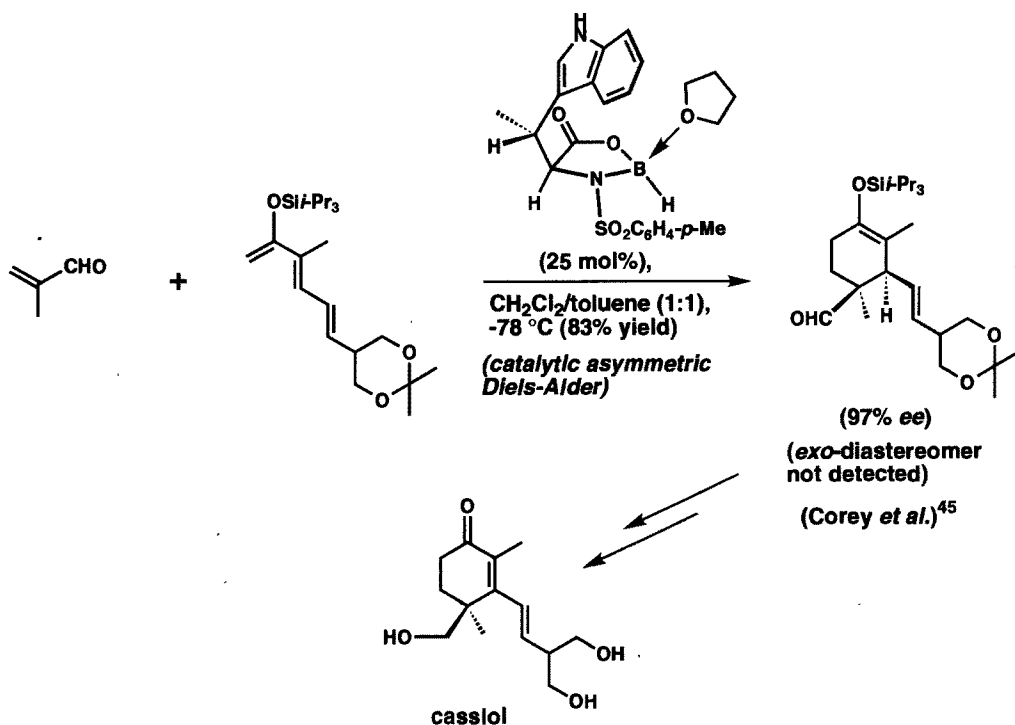
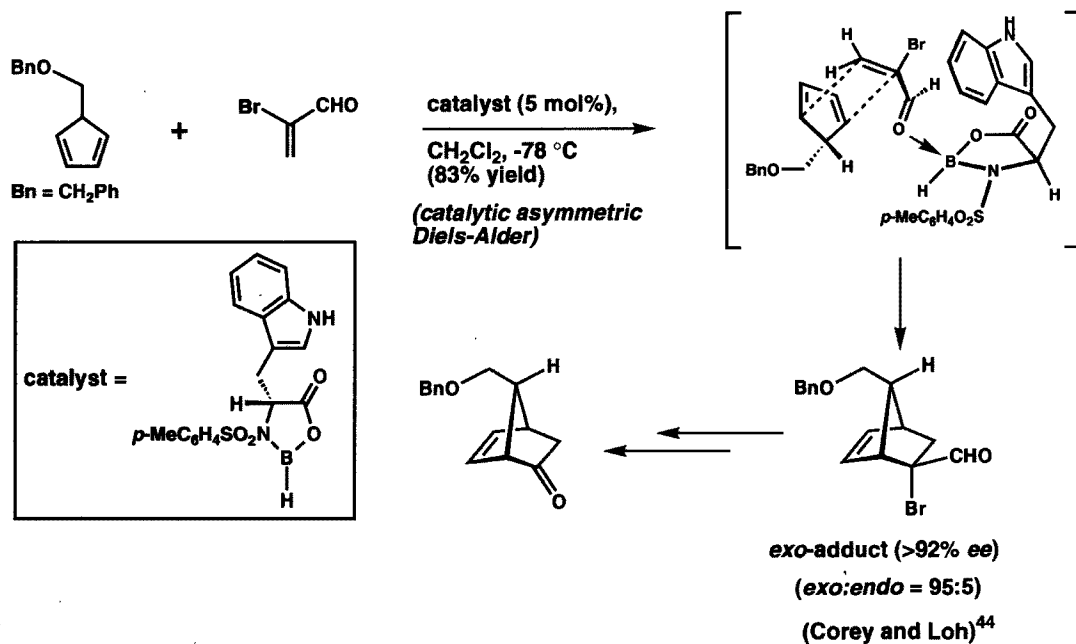
Scheme A11. Representative catalytic asymmetric reactions.



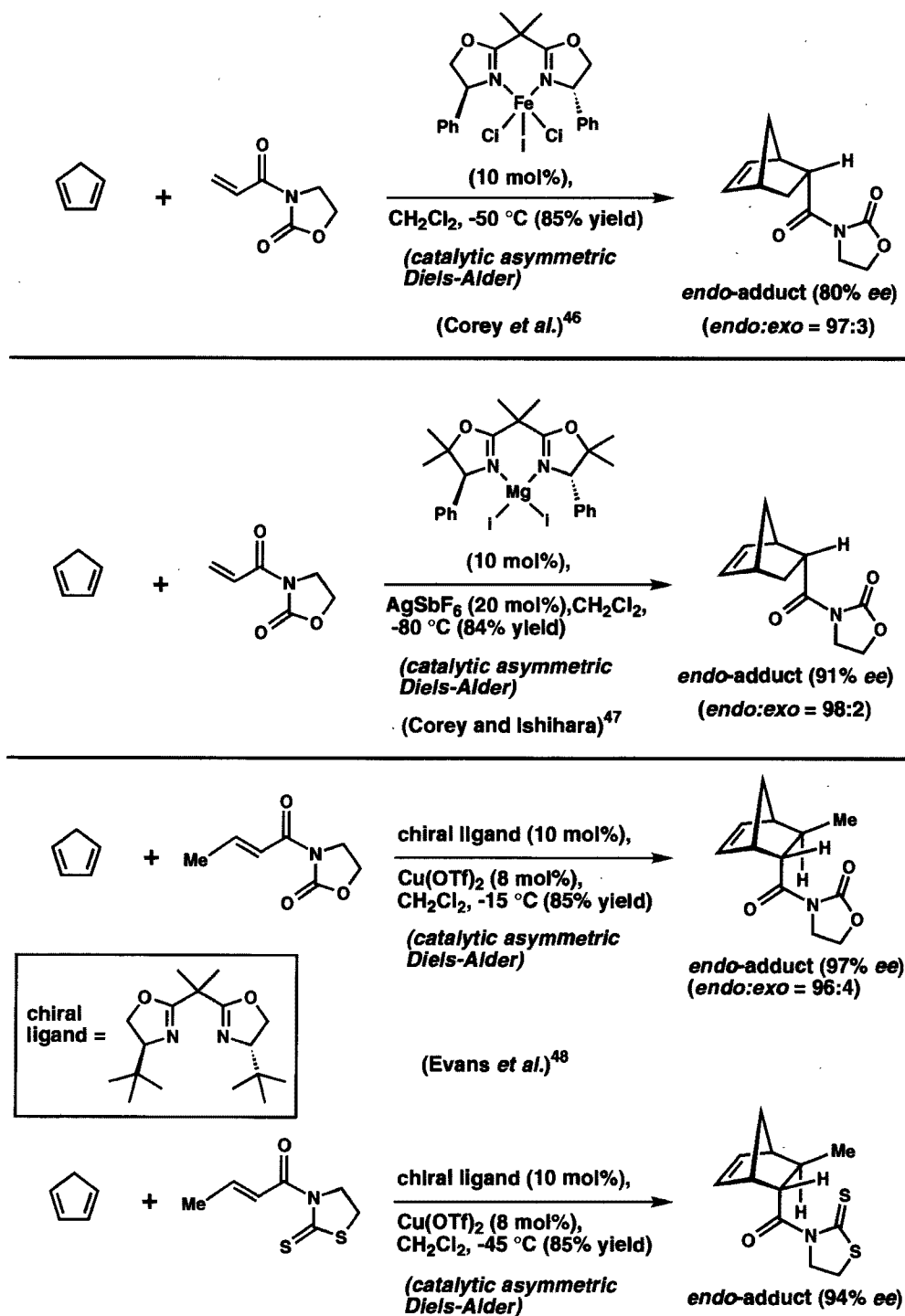
Scheme A12. Representative catalytic asymmetric reactions.



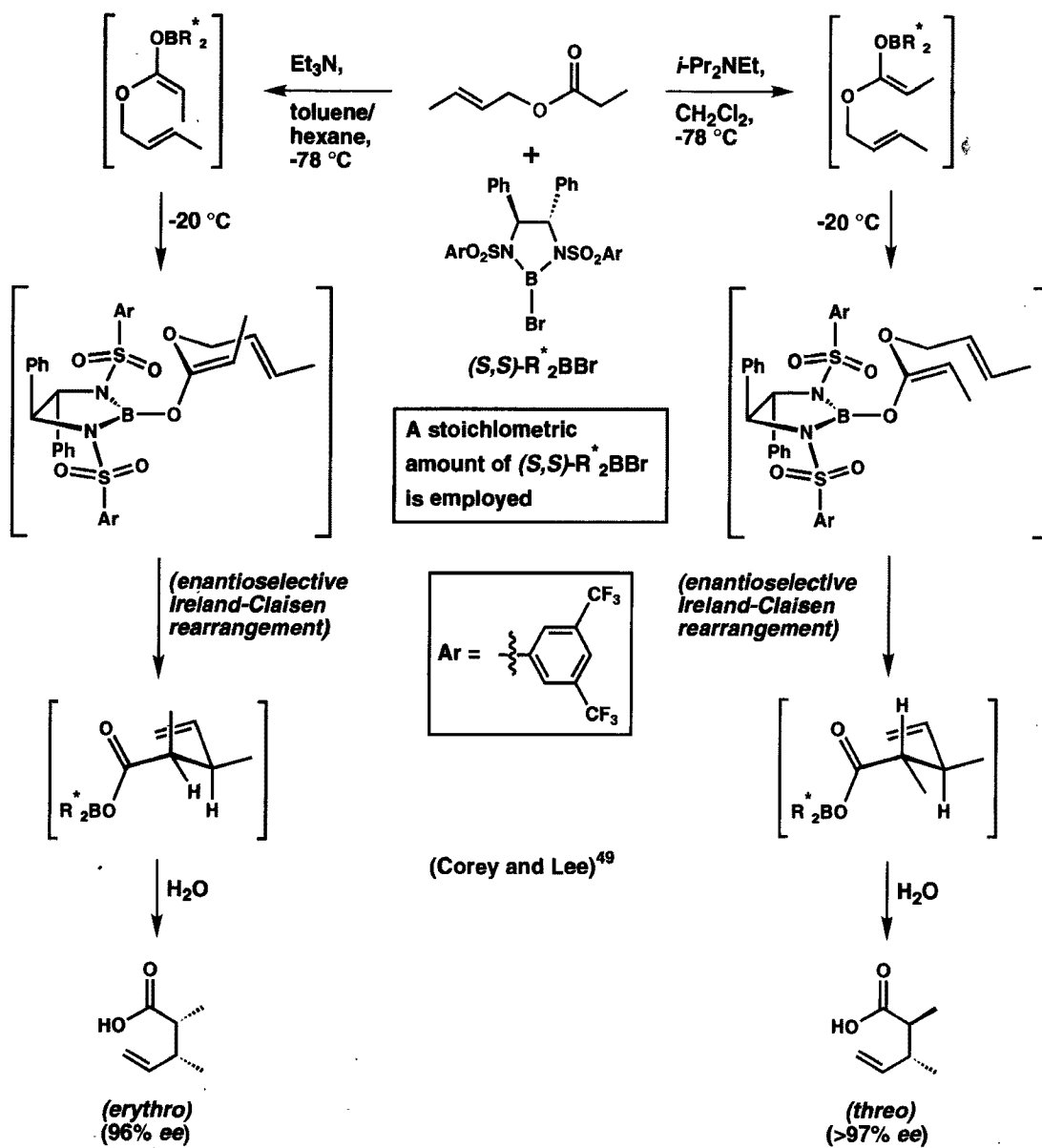
Scheme A13. Representative catalytic asymmetric reactions.



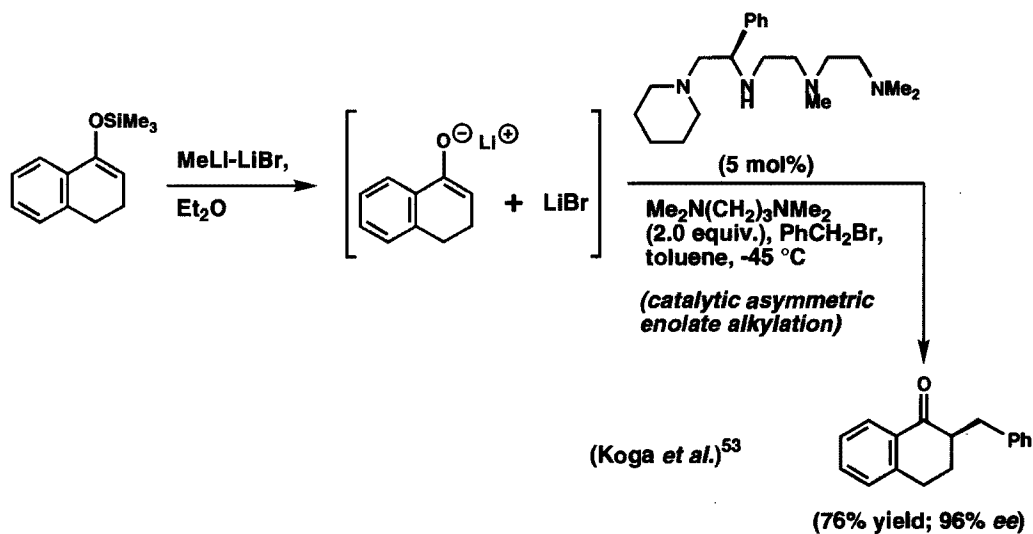
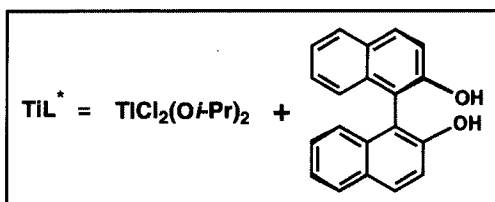
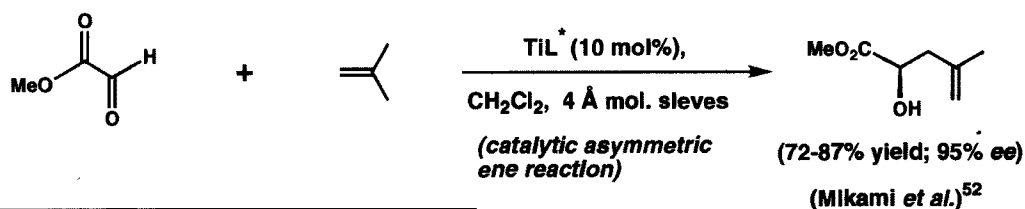
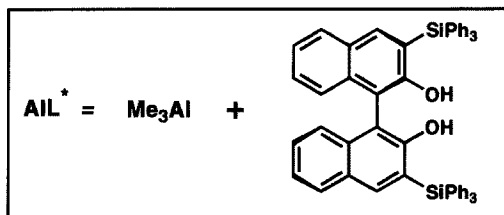
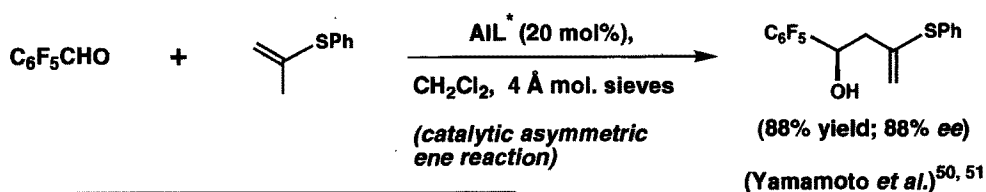
Scheme A14. Representative catalytic asymmetric reactions.



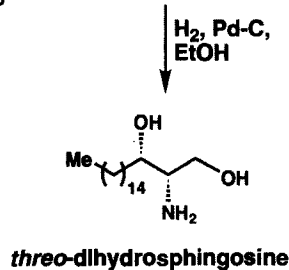
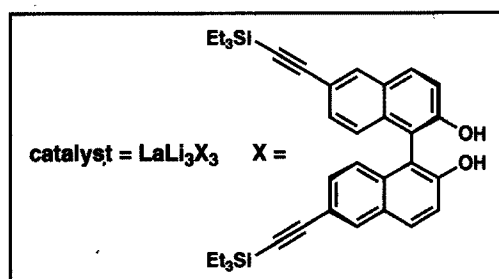
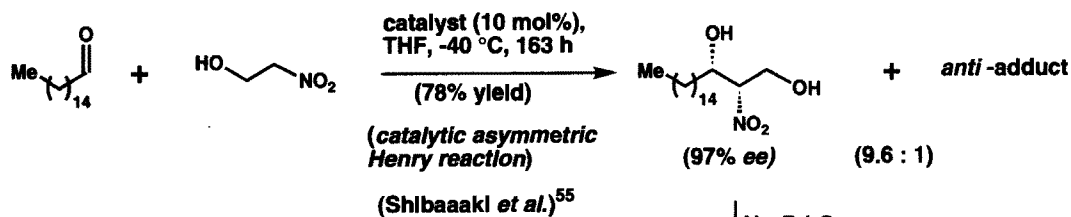
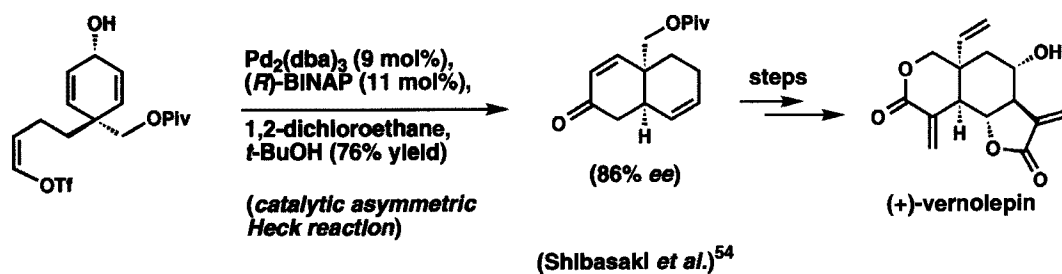
Scheme A15. Representative catalytic asymmetric reactions.



Scheme A16. Representative catalytic asymmetric reactions.



Scheme A17. Representative catalytic asymmetric reactions.

**Scheme A18.** Representative catalytic asymmetric reactions.

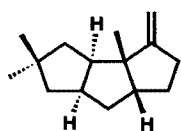
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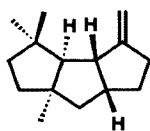
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1: hirsutene

2: $\Delta^{9(12)}$ -capnellene

D. P. Curran (1986)

Hirsutene and $\Delta^{9(12)}$ -Capnellene

23.1 Introduction

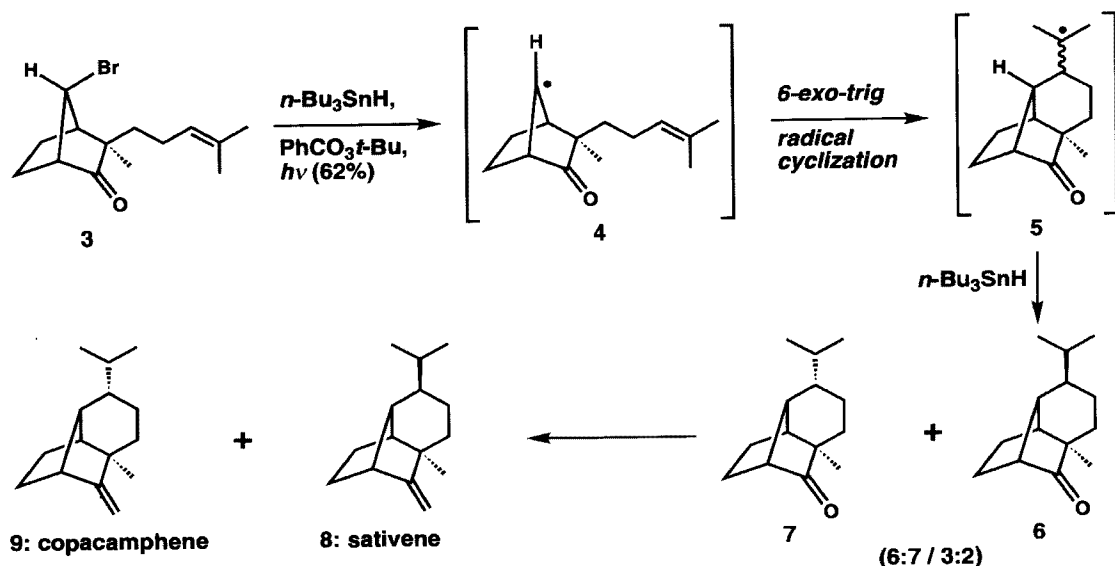
The central activity of organic synthesis is the construction of the carbon–carbon bond. For this purpose, a number of reaction processes have been developed, many of which feature the union of carbon nucleophiles (e.g. organometallic reagents) with carbon electrophiles (e.g. alkyl halides, alkyl sulfonates, epoxides, cyclic sulfates, carbonyl derivatives, and electrophilic olefins). Carbon–carbon bond constructions in the laboratory and in nature are, in fact, accomplished predominantly by polar reaction processes. In this regard, the central role of the carbonyl group as an electrophile and as an activator for the generation of nucleophilic enolate ions is particularly noteworthy. But in addition to polar processes, there are many nonpolar reactions that are indispensable as methods for carbon–carbon bond formation in organic synthesis. These include pericyclic reactions (i.e. electrocyclizations, sigmatropic rearrangements, and cycloadditions), photochemical reactions, and free radical reactions.¹

Although the value of polar processes and pericyclic reactions in the synthesis of carbon-containing molecules has long been recognized, synthetic organic chemists have been much more hesitant in the use of radical reactions for the construction of carbon–carbon bonds. It appears that much of this disinclination can be attributed to the notion that free radicals, because of their high reactivity, react in unselective, unpredictable ways. In most applications, the desired reaction course is but one of several competing paths. In radical chain processes, premature chain terminations

such as radical–radical couplings and hydrogen atom transfers are obvious alternative pathways by which a radical intermediate can react. The reaction pathway taken by a transient free radical intermediate is determined by a subtle balance of reaction rates.

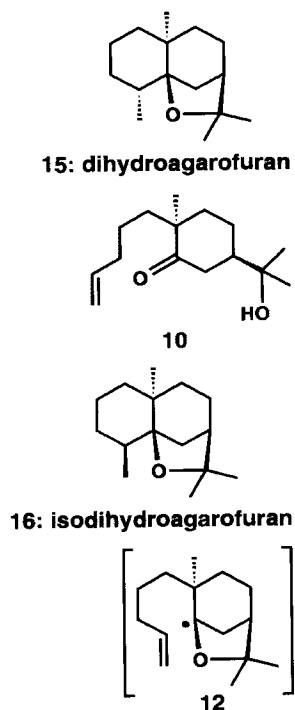
Nonetheless, the pioneering contributions of Walling, Ingold, Beckwith, Barton, Julia, Giese, and Stork, amongst others, have done much to debunk the myth that free radical reactions are too unmanageable to be of use in the synthesis of complex organic molecules.² Indeed, these pioneers have stimulated an explosive growth in the number of applications of radical-mediated carbon–carbon bond forming processes in organic synthesis.^{1,3} Although many intermolecular radical addition processes are successful and very useful, intramolecular radical additions or radical cyclizations have been shown to be of particular value in the arena of natural product total synthesis. Intermolecular radical addition processes that are plagued by rate problems can often be conducted, with much success, in the intramolecular mode. For example, intramolecular additions of carbon-centered radicals to substituted carbon–carbon, carbon–oxygen, and carbon–nitrogen multiple bonds can all be performed efficiently since the activation entropies of intramolecular radical additions are less negative than those of their intermolecular counterparts.^{3a} A decisive advantage of the intramolecular reaction mode is that highly hindered carbon–carbon bonds and quaternary stereogenic centers can be constructed through radical chemistry. In this chapter, the utility of radical reactions for the synthesis of structurally complex organic molecules is addressed, with an emphasis on some of the elegant synthetic work by D. P. Curran and his group at the University of Pittsburgh. Although only a few of the many noteworthy achievements in synthetic radical chemistry are discussed, we direct the readers' attention to some excellent, more substantial reviews of this important subject.^{1,3a,b,d}

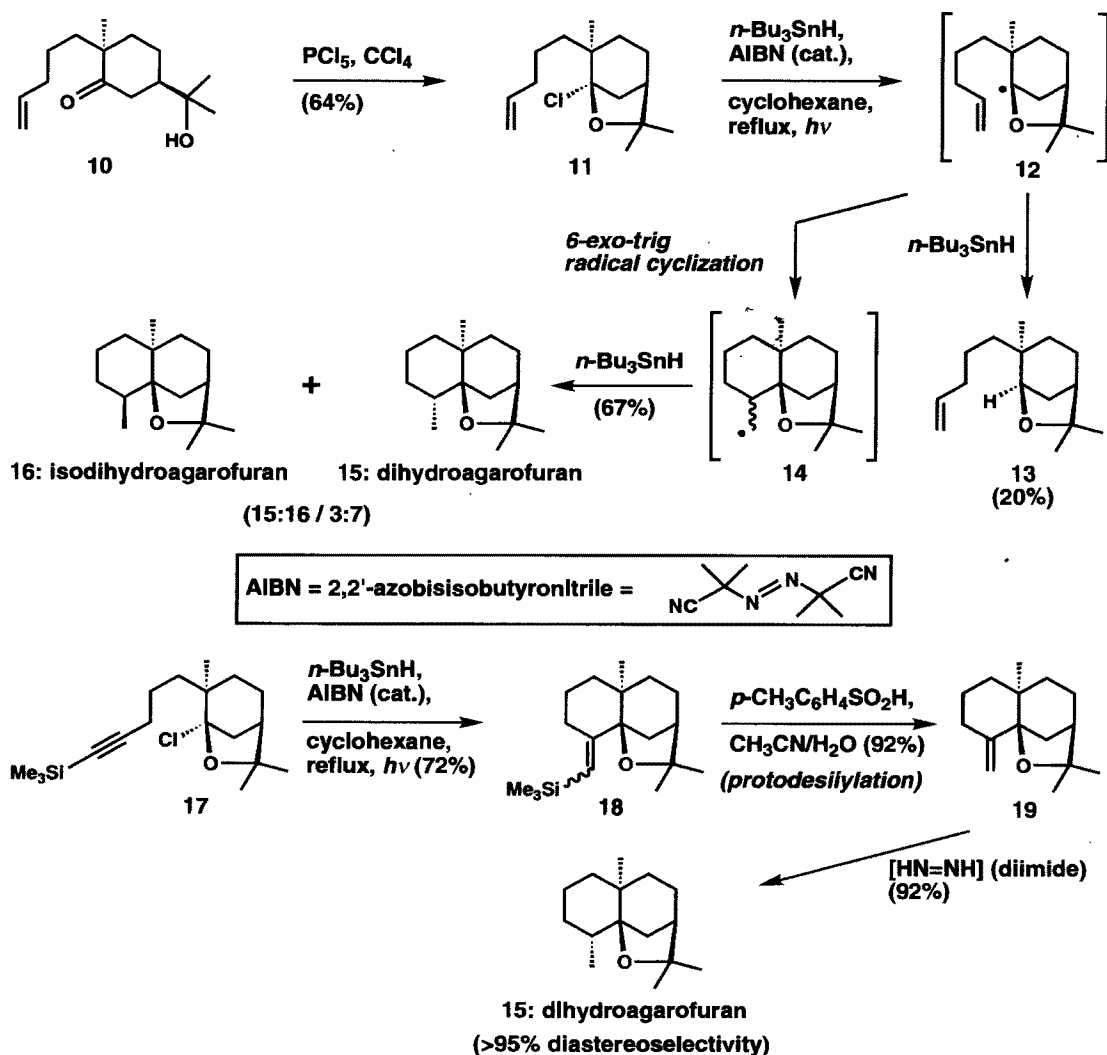
An early example of a free radical cyclization in natural product synthesis is found in the synthesis of the sesquiterpenes sativene (**8**) and copacamphene (**9**) by Bakuzis *et al.* (see Scheme 1).⁴ In the event, subjection of bromoketone **3** to the tin hydride method for radical generation results in the formation of a separable 3:2 mixture of diastereomeric tricyclic ketones **6** and **7** (62% total yield). In this transformation, the tri-*n*-butyltin radical (*n*-Bu₃Sn[•]) generated *in situ* abstracts the bromine atom (Br[•]) from **3** to give the transitory carbon-centered radical **4**. With a suitable radical acceptor six atoms removed, **4** can participate in a 6-*exo-trig* radical cyclization to give a new carbon-centered radical **5**, after which a terminating hydrogen atom transfer affords the two stereoisomeric products and regenerates *n*-Bu₃Sn[•]. Although the stereoselectivity of the radical cyclization is poor, it is noteworthy that a rather crowded carbon–carbon bond is constructed under mild, neutral reaction conditions. Ketone olefinations allowed the conversion of **6** and **7** to sativene (**8**) and copacamphene (**9**), respectively.



Scheme 1. Radical cyclization strategy for the synthesis of sativene (**8**) and copacamphene (**9**) by Bakuzis and coworkers.

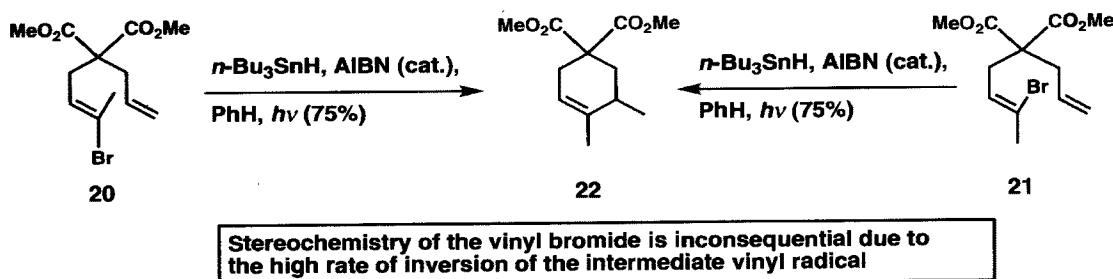
A challenging bond construction was also achieved in Büchi's synthesis of dihydroagarofuran (**15**), a constituent of galbanum resin (see Scheme 2).⁵ The action of phosphorus pentachloride on hydroxy ketone **10** in carbon tetrachloride results in the formation of bicyclic chloroether **11** in 64 % yield. With a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) as the radical initiator and tri-*n*-butyltin hydride (1.13 equiv), **11** is converted to a 3:7 mixture of diastereoisomeric substances, dihydroagarofuran (**15**) and isodihydroagarofuran (**16**) (67 % total yield). Uncyclized reduction product **13** is formed to the extent of 20 %. Under the reaction conditions, AIBN decomposes to two isobutyronitrile radicals $[(\text{CH}_3)_2\text{C}^\bullet\text{CN}]$ that abstract a hydrogen atom from tri-*n*-butyltin hydride, thus giving $n\text{-Bu}_3\text{Sn}^\bullet$; this is the initiation step. Once formed, $n\text{-Bu}_3\text{Sn}^\bullet$ abstracts the chlorine atom from **11** to give the putative bridgehead radical **12**. The latter species has two options available: **12** can abstract a hydrogen atom from tri-*n*-butyltin hydride to give the uncyclized reduction product **13**, or it can engage the pendant alkene in a radical cyclization to give a new carbon-centered radical **14**. Abstraction of a hydrogen atom from tri-*n*-butyltin hydride by **14** then affords the epimeric tricyclic products **15** and **16** and regenerates $n\text{-Bu}_3\text{Sn}^\bullet$. Not surprisingly, the ratio of uncyclized reduction product **13** to the cyclized products increases with increasing tri-*n*-butyltin hydride concentration.





Scheme 2. Büchi's radical cyclization strategy for the synthesis of dihydroagarofuran (15).

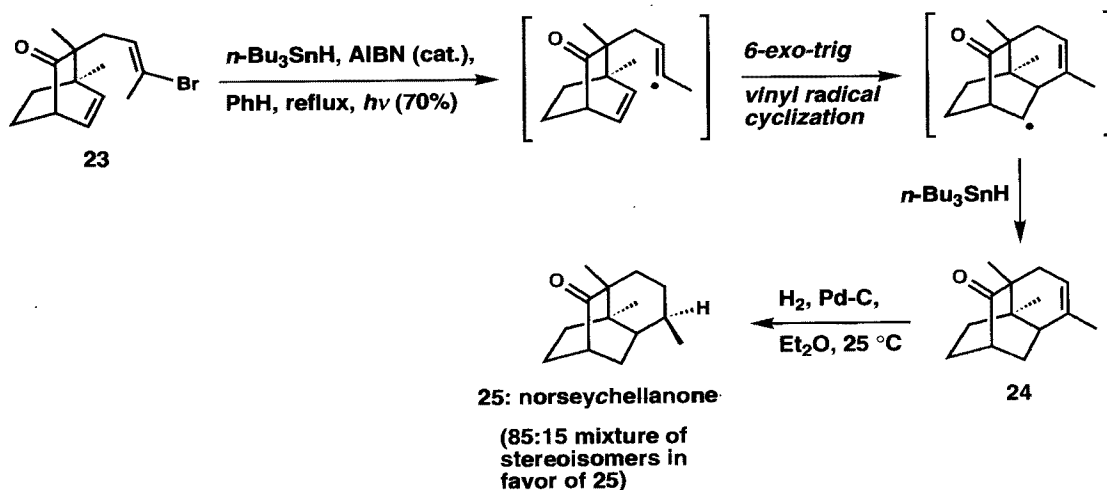
In an effort to identify a more stereoselective route to dihydroagarofuran (15), trimethylsilylated alkyne 17 was utilized as a substrate for radical cyclization (Scheme 2). Treatment of 17 with a catalytic amount of AIBN and tri-*n*-butyltin hydride (1.25 equiv) furnishes a mixture of stereoisomeric vinyl silanes 18 (72% combined yield) along with an uncyclized reduction product (13% yield). The production of stereoisomeric vinyl silanes in this cyclization is inconsequential because both are converted to the same alkene 19 upon protodesilylation. Finally, a diastereoselective diimide reduction of the double bond in 19 furnishes dihydroagarofuran



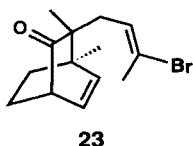
Scheme 3. Selected vinyl radical cyclizations developed by Stork and coworkers.

furan (**15**) in 92 % yield, contaminated with less than 5 % of epimer **16**. The impressive stereoselectivity exhibited in this reduction was attributed to the directing effect of the proximal ether oxygen.⁶

Vinyl radicals can also participate in 6-*exo* cyclizations. In pioneering work, Stork and his group at Columbia University showed that stereoisomeric vinyl bromides **20** and **21** (see Scheme 3) can be converted to cyclohexene **22**.⁷ The significance of this finding is twofold: first, the stereochemistry of the vinyl bromide is inconsequential since both stereoisomers converge upon the same product; and second, the radical cyclization process tolerates electrophilic methoxycarbonyl groups. The observation that the stereochemistry of the vinyl bromide is inconsequential is not surprising because the barrier for inversion of most vinyl radicals is very low.⁸ This important feature of vinyl radical cyclization chemistry is also exemplified in the conversion of vinyl bromide **23** to tricycle **24**, the key step in Stork's synthesis of norseychellanone (**25**) (see Scheme 4).⁹ As in

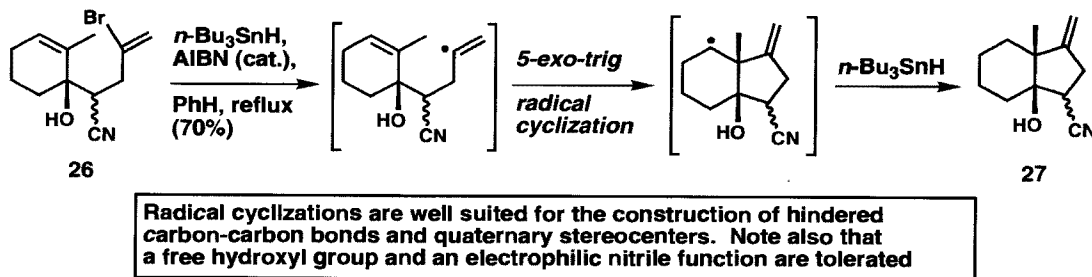


Scheme 4. Stork's vinyl radical cyclization strategy for the synthesis of norseychellanone (**25**).



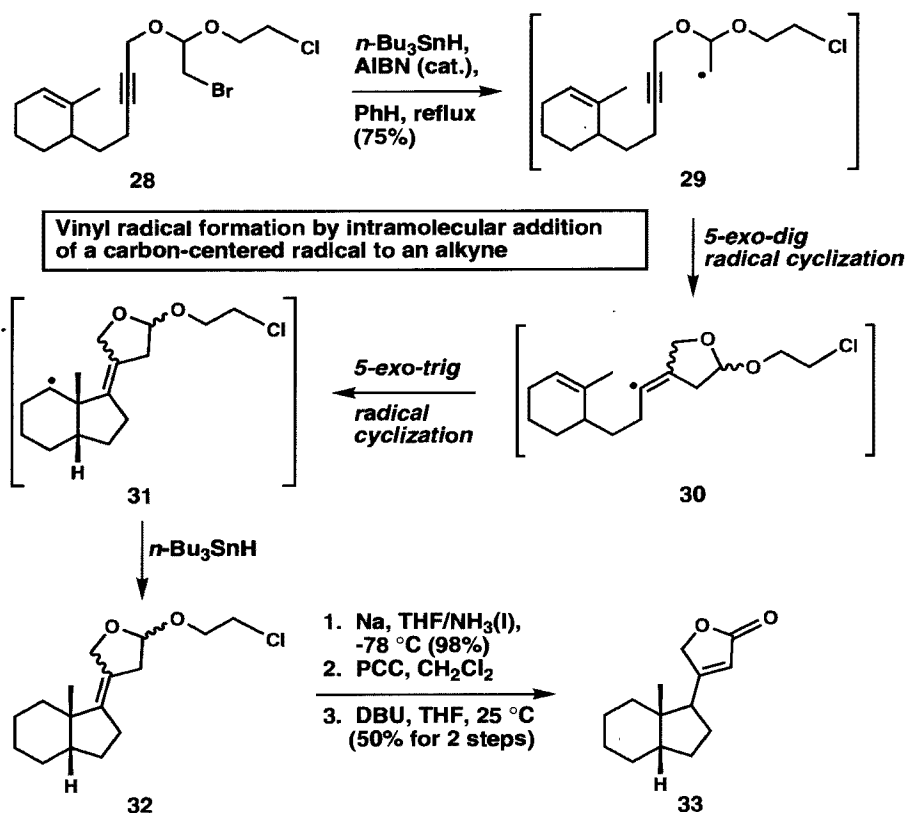
the cyclizations shown in Scheme 3, the stereochemistry of the vinyl bromide function in **23** is irrelevant. It is also noteworthy that an electrophilic keto group is compatible with the radical cyclization. By contrast to ionic processes, radical reactions display remarkable chemoselectivities. Although carbon-centered radicals can, in certain contexts, add efficiently to aldehyde carbonyls,¹⁰ the rates at which carbon radicals react with the carbonyl groups of ketones and esters tend to be very slow owing to the strength of the carbon–oxygen π bond. Such functional groups can, therefore, be tolerated in most radical reactions in marked contrast to polar processes. Although carbon-centered radicals are highly reactive intermediates, high levels of chemo-, regio-, and even stereoselectivity can be achieved because radical additions proceed under mild reaction conditions.^{3d}

The reactions of carbon-centered radicals are also tolerant of free hydroxyl or amino groups. In a historically significant example, the Stork group demonstrated that vinyl bromide **26** (see Scheme 5), on treatment with tri-*n*-butyltin hydride and a catalytic amount of AIBN in refluxing benzene, is converted to methyleneindanol **27** in 70 % yield. In this transformation, the vinyl radical derived from **26** engages the double bond in the proximate ring in a radical cyclization; a crowded carbon–carbon bond and a quaternary stereocenter are formed smoothly. Indeed, one of the most valuable assets of radical cyclization methodology is that hindered carbon–carbon bonds and quaternary stereocenters can be constructed efficiently. It is also noteworthy that the carbon–carbon double bond of the newly formed ring occupies a predefined position and is poised for further elaboration if desired. Moreover, neither the electrophilic nitrile function, nor the free hydroxyl group interferes with the desired radical cyclization. Free hydroxyl and amino groups are preserved in radical reactions due to the strong resistance of O–H and N–H bonds to homolytic cleavage. On the basis of the examples surveyed so far, it may be concluded that radical addition processes are compatible with a diversity of functional groups and are thus ideally suited for the synthesis of multifunctional molecules.

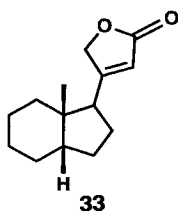


Scheme 5. Stork's construction of methyleneindanol **27**.

Although vinyl radicals are conveniently generated by reaction of a vinyl halide with a stannyl radical, the Stork group reported an intriguing alternative that features the intramolecular addition of a carbon-centered radical to an alkyne. In an elegant example, treatment of mixed acetal **28** (see Scheme 6) with tri-*n*-butyltin hydride and a catalytic amount of AIBN in refluxing benzene furnishes tricycle **32** in 75% yield.¹¹ In this transformation, *n*-Bu₃Sn• selectively abstracts the bromine atom from **28**. The resulting transient carbon-centered radical **29** then adds regioselectively to the proximate alkyne function, generating vinyl radical **30**. Despite the hindered nature of its cyclohexene double bond, **30** participates in a 5-*exo-trig* radical cyclization to give cyclohexyl radical **31**. Finally, abstraction of a hydrogen atom from tri-*n*-butyltin hydride by **31** produces tricycle **32** and regenerates *n*-Bu₃Sn•. Two carbon-carbon bonds, two rings, and a congested quaternary stereocenter are created in this productive tandem radical bicyclization. Reductive cleavage of the chloroethyl protecting group in **32** with sodium in



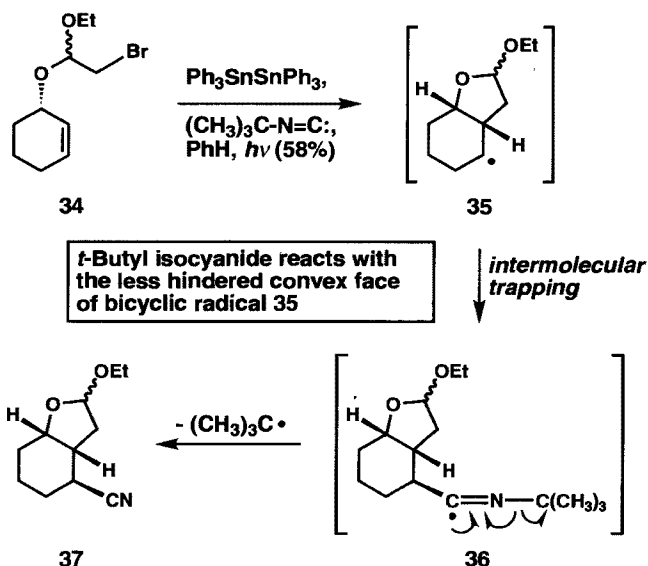
Scheme 6. Stork's synthesis of butenolide **33**.



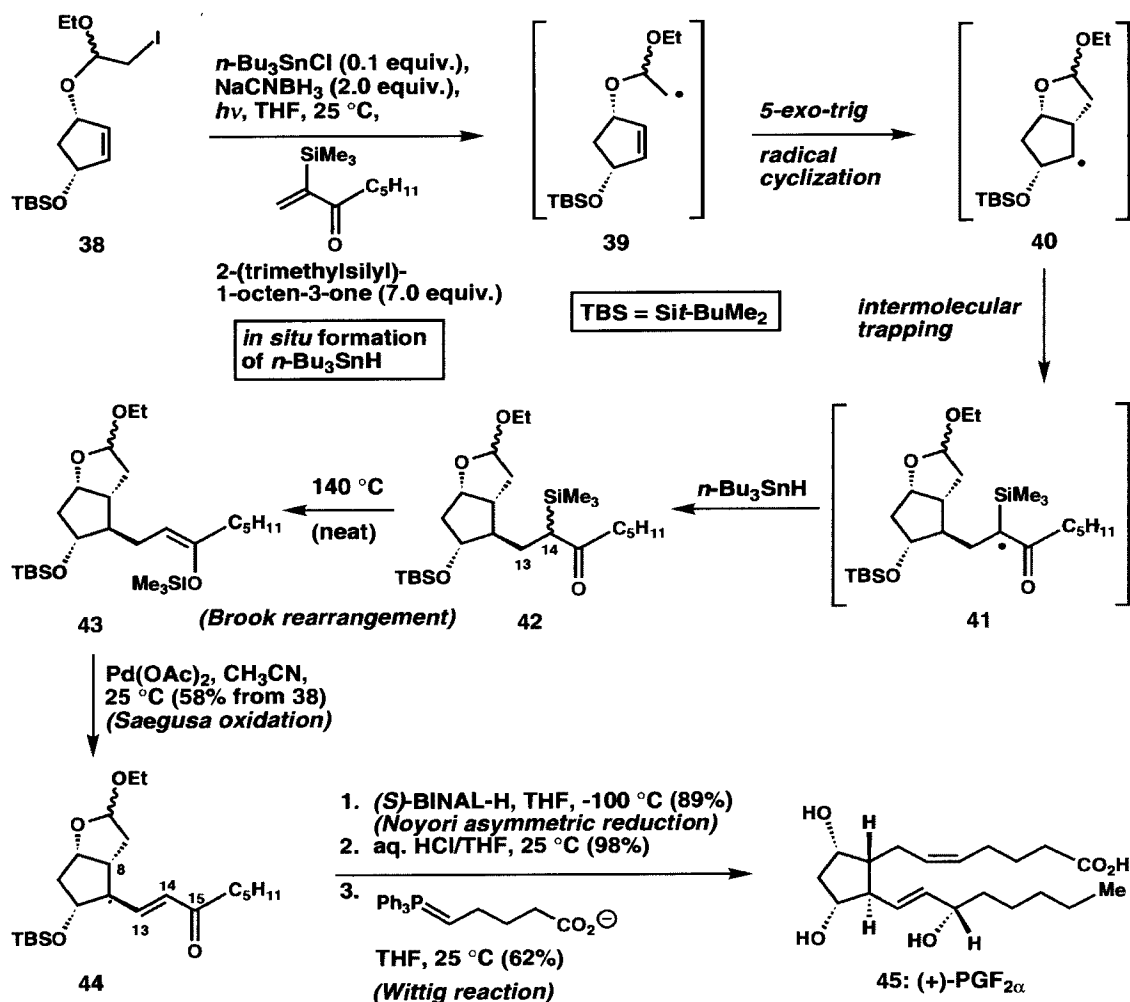
THF/liq. NH_3 , followed sequentially by oxidation and base-induced double bond isomerization, provides butenolide **33**, a compound that possesses the lactone system of the steroidal cardiac aglycones.

The finding that a carbon-centered radical produced by a radical cyclization can be intercepted intermolecularly by an entity other than hydrogen constitutes a major development in synthetic radical chemistry. In many cases, it would be desirable to terminate a radical chain process with a grouping that would be amenable to future synthetic manipulations. In a pioneering example, Stork and Sher demonstrated that carbon-centered radical **35** (see Scheme 7), the product of a 5-*exo-trig* radical cyclization of bromoacetal **34**, can be trapped with *tert*-butylisocyanide.¹² As expected, *tert*-butyl isocyanide engages the less hindered convex face of bicyclic radical **35**. Presumably in the manner shown, a chemically versatile cyano group is introduced and *tert*-butyl radical is eliminated. The overall process accomplishes a tandem vicinal difunctionalization of an alkene, and its productivity is analogous to the familiar conjugate addition of a carbon nucleophile to an enone, followed by trapping of the resulting enolate ion by a suitable electrophile.¹³ Incidentally, if tri-*n*-butyltin hydride is used as the tin radical precursor instead of hexaphenylditin, a hydrogen atom transfer from tri-*n*-butyltin hydride to **35** is the exclusive pathway; no trapping of **35** by *tert*-butylisocyanide occurs.

The promising transformation shown in Scheme 7 and some subsequent studies¹⁴ provided the basis for an elegant synthesis of (+)-prostaglandin $\text{F}_{2\alpha}$ [(+)- $\text{PGF}_{2\alpha}$] (**45** in Scheme 8).¹⁵ In the crucial

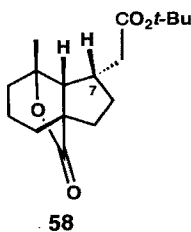
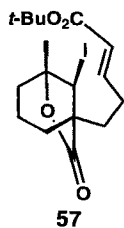
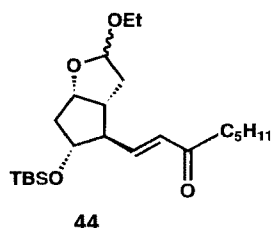
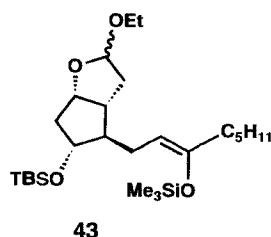
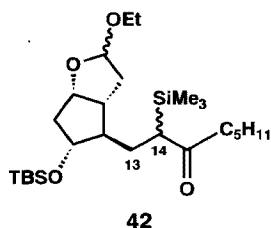


Scheme 7. Stork's tandem vicinal difunctionalization strategy.



Scheme 8. Stork's tandem radical cyclization/trapping strategy for the synthesis of (+)-prostaglandin $F_{2\alpha}$ (45).

step, iodoacetal **38**, readily available in optically active form, is converted to α -trimethylsilylated ketone **42** by way of a tandem radical cyclization/intermolecular trapping process. In one step, two differentiated carbon appendages are added across a carbon-carbon double bond in a completely regio- and stereoselective manner. The allylic acetal oxygen of the initial radical **39** controls the regio- and stereochemical course of the radical cyclization to **40**. Once formed, **40** reacts efficiently and diastereoselectively with 2-(trimethylsilyl)-1-octen-3-one, a reactive radical acceptor, to give **41**; the cup-shaped structure of bicyclic radical **40** and the α -disposed

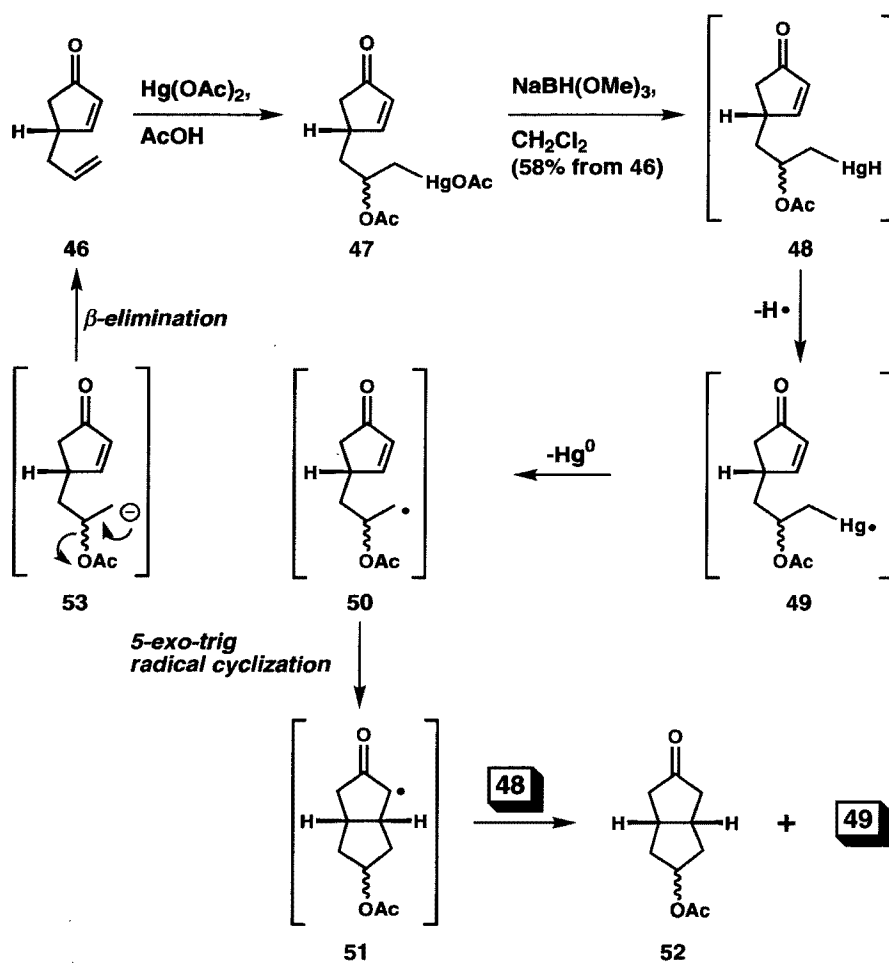


tert-butyldimethylsilyl ether mutually reinforce the indicated (and desired) stereochemical outcome of the intermolecular radical alkylation step. A terminating hydrogen atom transfer then completes the construction of **42**.

The trimethylsilyl grouping is a valuable feature of **42** because it allows the *trans*- $\Delta^{13,14}$ double bond of PGF_{2 α} to be introduced regioselectively. To this end, a thermally induced Brook rearrangement¹⁶ converts **42** to trimethylsilyl enol ether **43**, a substance which undergoes conversion to α,β -unsaturated ketone **44** on treatment with palladium(II) acetate in acetonitrile (Saegusa oxidation)¹⁷ (58% overall yield from **38**). After a stereoselective Noyori reduction¹⁸ of the C-15 ketone carbonyl in **44**, treatment with aqueous acid hydrolyzes the cyclic acetal moiety and cleaves the *tert*-butyldimethylsilyl ether. Finally, a *cis*-stereoselective Wittig reaction between the newly formed lactol and the indicated phosphorus ylide introduces the remaining carbons of the C-8 side chain and completes the total synthesis of (+)-PGF_{2 α} (**45**).

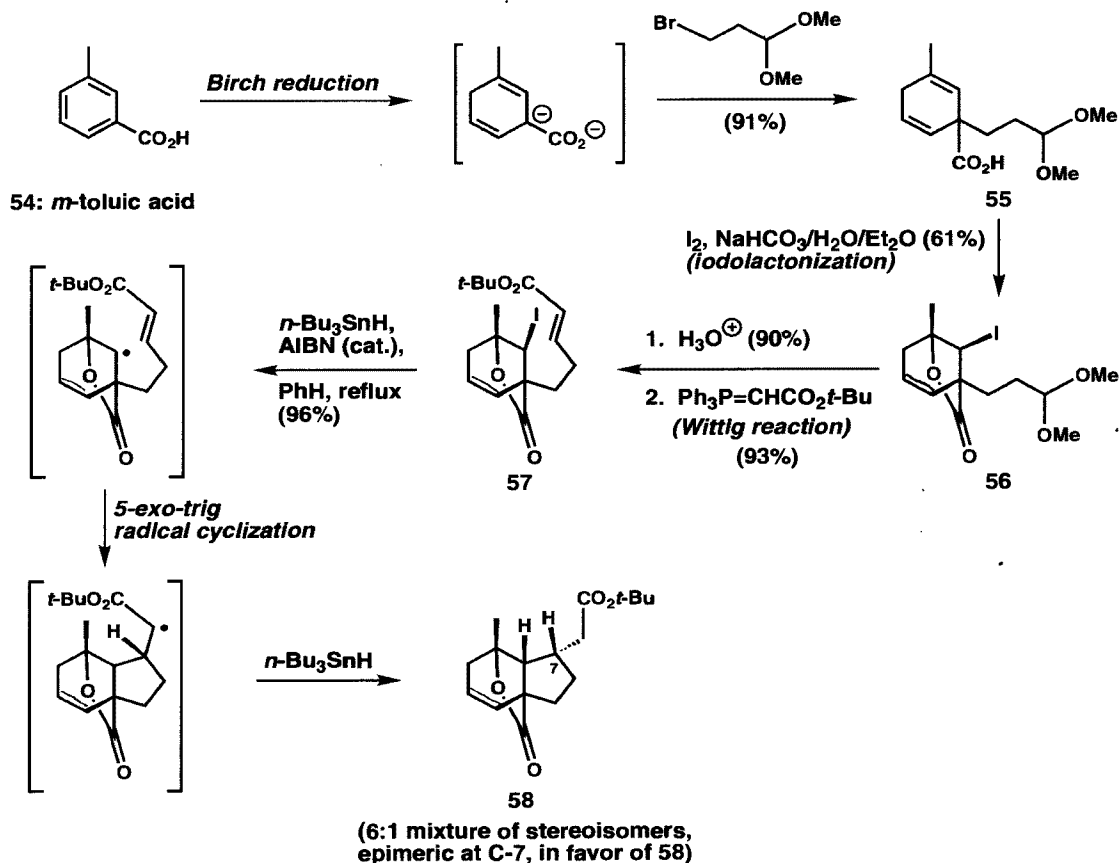
Radical reactions can create carbon-carbon bonds that would be very difficult or impossible to construct using traditional polar processes. For example, using Giese's reductive mercury method,^{3a,19} Danishefsky et al. demonstrated that organomercury compound **47** (see Scheme 9), the product of an acetoxymercuration of dienone **46**, can be converted to bicyclo[3.3.0]octane **52** (58% yield from **46**).²⁰ According to the accepted mechanism, sodium trimethoxyborohydride reduces organomercuric acetate **47** to give mercuric hydride **48**. Homolytic cleavage of the mercury-hydrogen bond then produces organomercury radical **49**, which fragments to give β -acetoxy radical **50**. With a reactive enone double bond and a carbon-centered radical in proximity, **50** undergoes radical cyclization to a new carbon-centered radical **51**. The latter intermediate abstracts a hydrogen atom from **48**, affording the bicyclic product **52** and regenerating organomercury radical **49**. This process combines the simplicity of alkene solvomercuration with an efficient reductive radical cyclization. It is worth emphasizing that any attempt to construct the same carbon-carbon bond through a polar process involving the hypothetical carbanion **53** (Scheme 9) would most likely be thwarted by a destructive, irreversible β -elimination of the newly introduced acetoxy function to give **46**. A valuable attribute of radical reactions is that OR and NR₂ groups in the β -position are not eliminated.

The success of intramolecular conjugate additions of carbon-centered radicals in multifunctional contexts is noteworthy. Compound **57** (see Scheme 10), prepared by an interesting sequence starting from *meta*-toluic acid (**54**) (see **54** \rightarrow **55** \rightarrow **56** \rightarrow **57**), can be converted to the highly functionalized perhydroindane **58** through an intramolecular conjugate addition of a hindered secondary radical.^{21,22} This radical cyclization actually furnishes a 6:1 mixture of perhydroindane diastereoisomers, epimeric at C-7, in favor of **58** (96% total yield). It should be noted that a substantially less strained *cis*-fused bicyclo[4.3.0] substructure is formed in this cyclization.



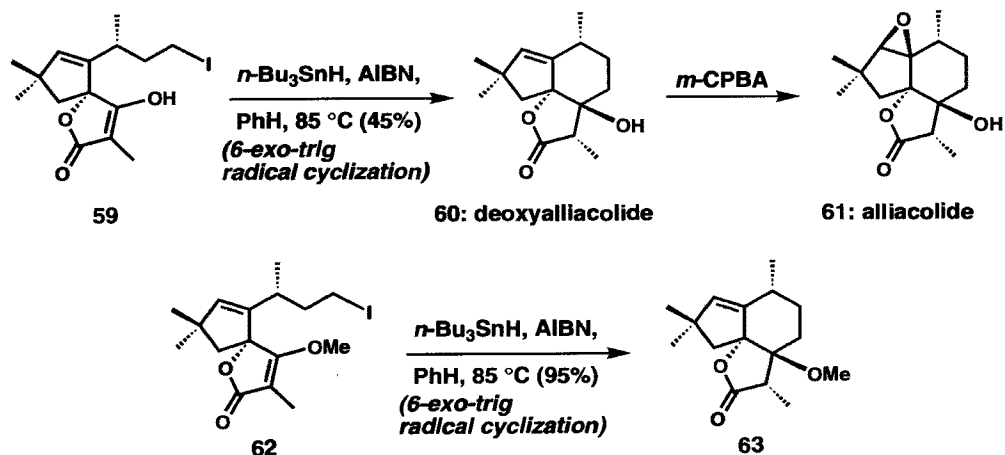
In contrast to carbanions, carbon-centered radicals tolerate oxygenated functionality in the β -position

Scheme 9. Danishefsky's synthesis of bicyclo[3.3.0]octane **52** using Giese's reductive mercury method.

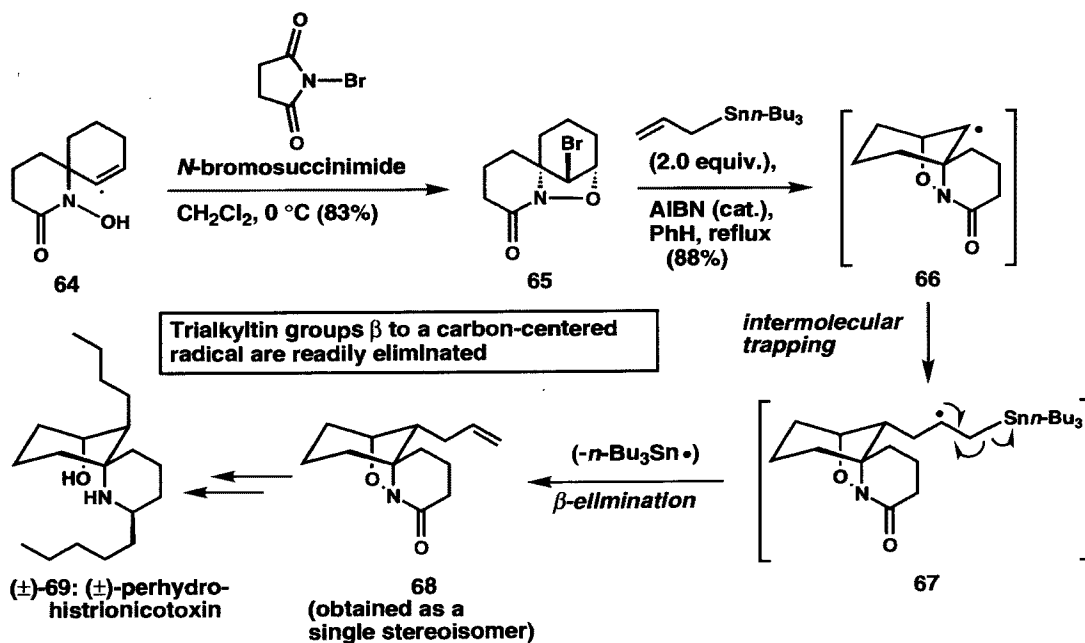


Scheme 10. Intramolecular free radical conjugate addition in Hart's synthesis of perhydroindane **58**.

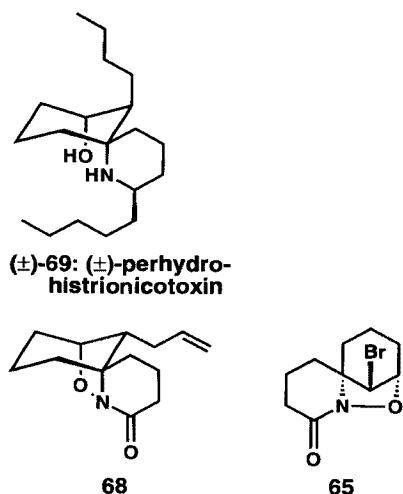
More recently, Pattenden and his group utilized a 6-*exo-trig* intramolecular conjugate addition of a carbon-centered radical in a synthesis of the tetracyclic lactone alliacolide (**61**) (see Scheme 11).²³ Although compound **59** has two carbon-carbon double bonds in proximity to the iodine-bearing carbon, the lactone-activated double bond is much more reactive as a radical acceptor (lower lying LUMO)²⁴ than the unconjugated double bond. On treatment with tri-*n*-butyltin hydride and AIBN in benzene at 85 °C, compound **59** is converted diastereoselectively to deoxyalliacolide (**60**) (45% yield). Interestingly, compound **62** cyclizes much more smoothly than **59**, affording tricyclic lactone **63** as a single diastereoisomer in 95% yield. It is noteworthy that lactone activation of the rather hindered double bond permits the smooth formation of a fully substituted stereogenic center in this transformation. Moreover, the neutral reaction medium tolerates oxygenated functionality and does not induce a destructive β -elimination of the methoxyl group.



Scheme 11. Intramolecular free radical conjugate addition in Pattenden's synthesis of alliacolide (**61**).

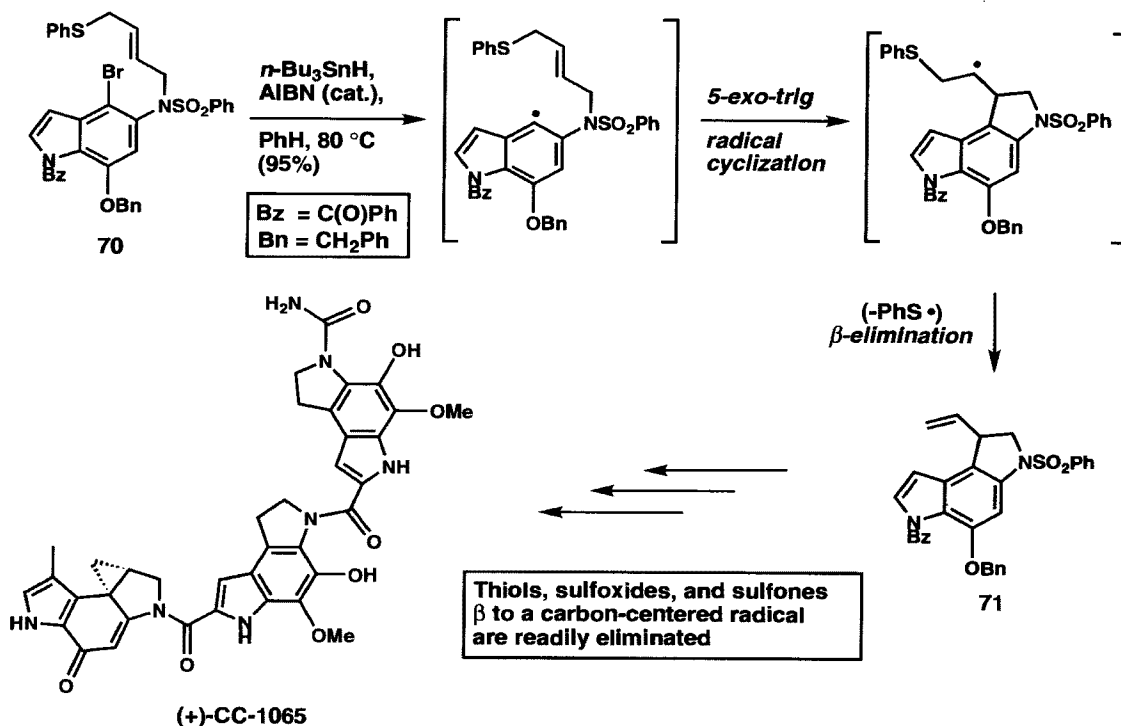


Scheme 12. Intermolecular radical trapping-fragmentation in Keck's synthesis of (\pm) -perhydrohistrionicotoxin [(\pm)-**69**].



The tolerance of carbon-centered radicals for OR and NR₂ groups in the β -position is a virtue of radical reactions. Nonetheless, some groupings (e.g. halogens, thiols, sulfoxides, sulfones, and trialkylstannanes) are readily eliminated. An elegant example is found in Keck's synthesis of (±)-perhydrohistrionicotoxin [(±)-**69**] (see Scheme 12).²⁵ In a key step, bromide **65**, produced by the action of *N*-bromosuccinimide on compound **64**, is stereoselectively converted to the allylated tricycle **68** in 88% yield. In this interesting transformation, *n*-Bu₃Sn[•] generated *in situ*, abstracts Br[•] from **65**, affording transitory carbon-centered radical **66**. Intermolecular addition of **66** to allyl tri-*n*-butylstannane then gives a new carbon radical **67** which spontaneously fragments, expelling *n*-Bu₃Sn[•] and generating the C-allylated product **68**. The extruded tri-*n*-butyltin radical is available for reaction with bromide **65** (chain propagation). Gratifyingly, allylation of neopentyl radical **66** is not undermined by a destructive β -elimination of either oxygen or nitrogen.

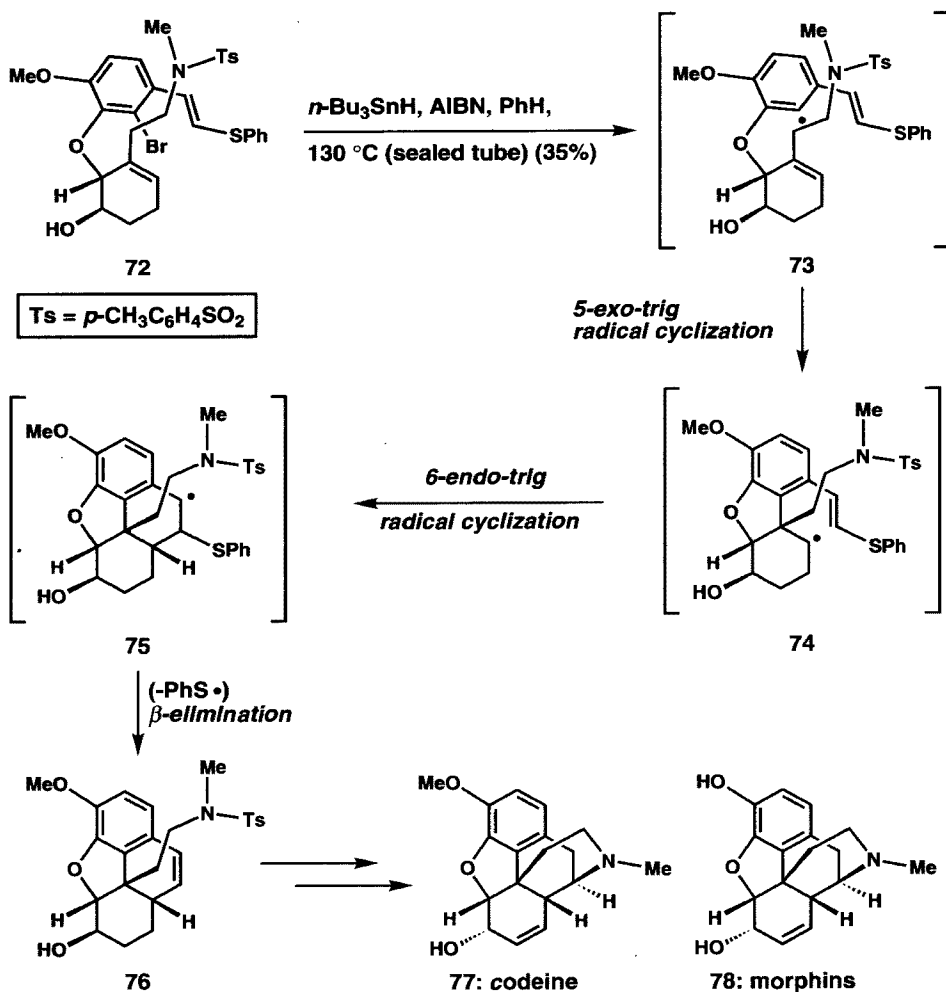
An interesting free radical carbon-carbon bond formation with concomitant elimination of a β -thio substituent was achieved during the course of Boger's impressive synthesis of CC-1065.^{26,27} In the event, treatment of aryl bromide **70** (see Scheme 13) with tri-*n*-



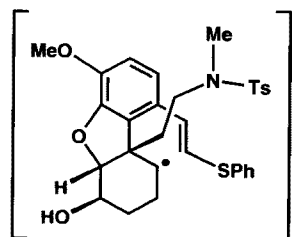
Scheme 13. Intramolecular radical addition/fragmentation in Boger's synthesis of (+)-CC-1065.

butyltin hydride and AIBN results in the formation of vinyl indoline **71** in 95% yield by a radical addition/fragmentation mechanism.²⁸ A valuable feature of this type of bond-forming strategy is that the newly fashioned carbon–carbon double bond in the product provides convenient opportunities for further elaboration.

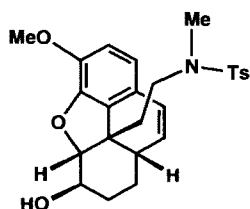
The β -elimination of a thiyl radical (RS^\bullet) terminated a remarkably productive tandem radical bicyclization in Parker's formal total syntheses of (\pm)-codeine and (\pm)-morphine (see Scheme 14).²⁹ Subjection of aryl bromide **72** to the conditions indicated generates transient aryl radical **73**, an intermediate which engages the substi-



Scheme 14. Tandem radical bicyclization–fragmentation in Parker's synthesis of intermediate **76** en route to codeine (**77**) and morphine (**78**).



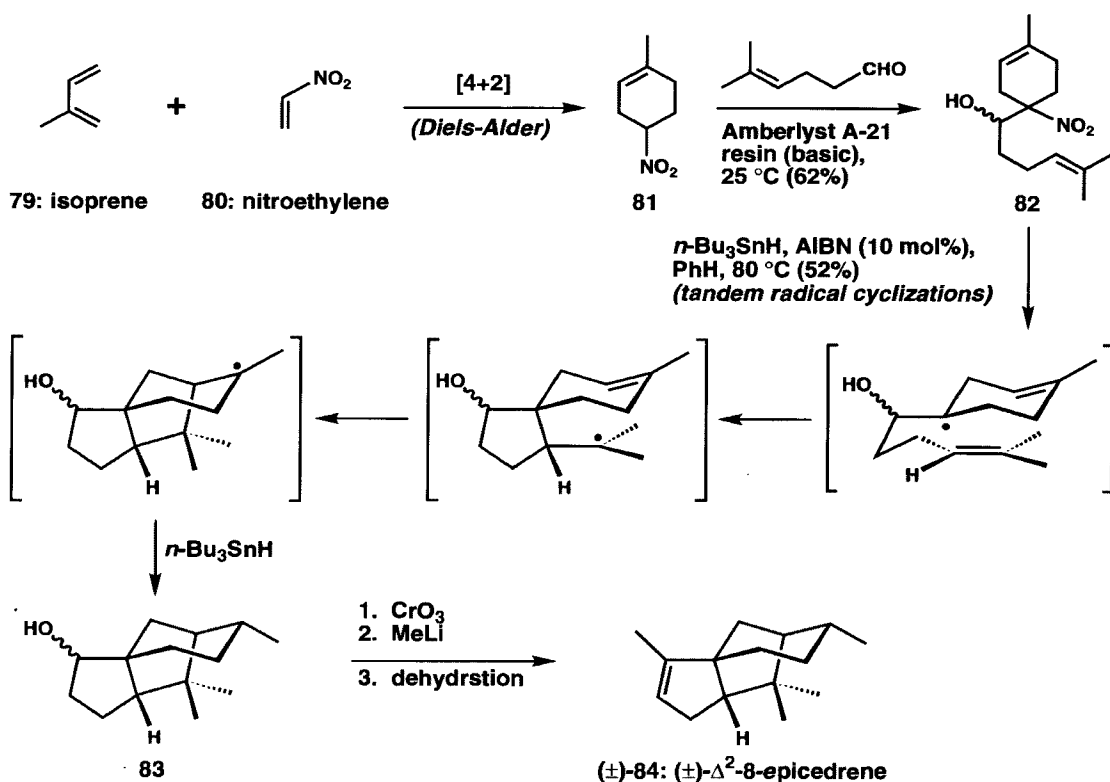
74



76

tuted cyclohexene double bond in a stereo- and regioselective 5-*exo-trig* radical cyclization. This event creates a new carbon-centered radical **74** which then participates in a 6-*endo-trig* cyclization with the pendant styryl double bond to give benzylic radical **75**. Finally, spontaneous β -elimination of PhS^\bullet occurs, affording key intermediate **76** (35% yield). Two rings, a critical quaternary stereocenter, and a strategically placed carbon-carbon double bond are all formed in this elegant sequential transformation.

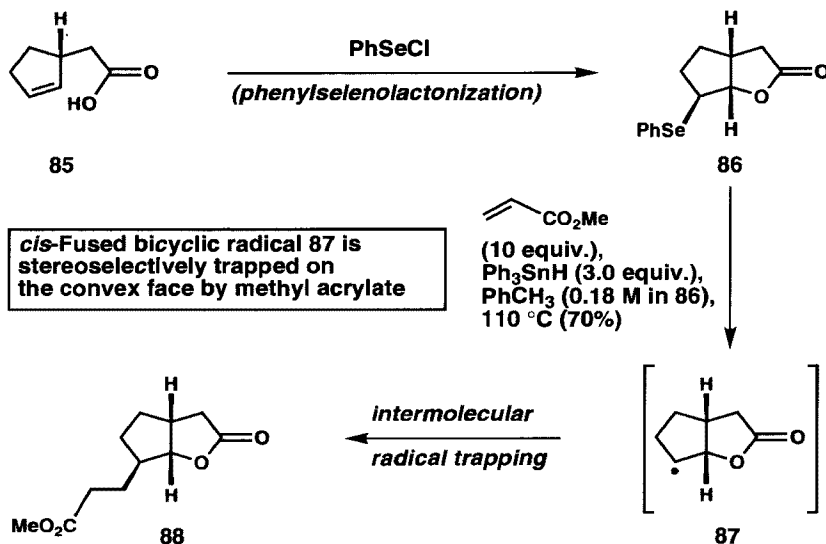
Sequential radical cyclizations are also featured in an efficient and clever synthesis of the cedrane framework **83** (see Scheme 15).³⁰ Compound **81**, the product of a regioselective Diels-Alder reaction between isoprene (**79**) and nitroethylene (**80**), participates in a nitroaldol reaction (Henry reaction) with 5-methyl-4-hexenal in the presence of a basic resin to give **82**. Because the nitro group in **82** is attached to a tertiary carbon atom, it can serve as a precursor to a carbon-centered radical. Thus, on treatment with tri-*n*-butyltin hydride and AIBN, **82** is converted to tricyclo[5.3.1.0^{1,5}]undecane **83** by the tandem radical cyclizations shown (52% yield). Conventional manipulations then complete the synthesis of (\pm) - Δ^2 -8-epicedrene



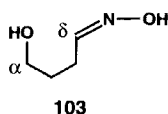
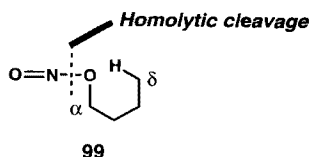
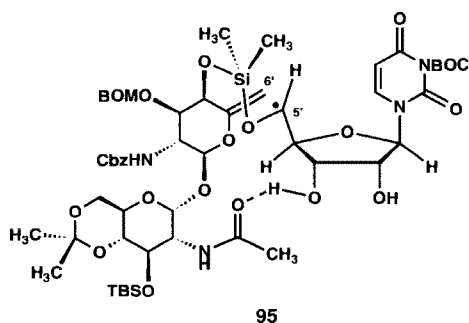
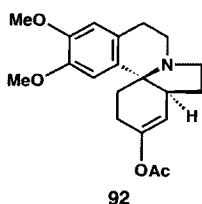
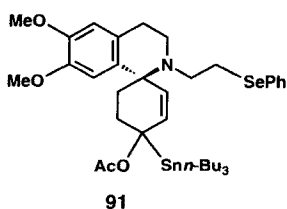
Scheme 15. Tandem radical cyclizations in Chen's synthesis of (\pm) - Δ^2 -8-epicedrene [(\pm)-**84**].

drene [(±)-**84**]. This impressively short synthesis of a small, yet complicated, tricycle (see **83**) takes full advantage of the versatile nitro group.³¹ In the first step, isoprene (**79**) and nitroethylene (**80**) combine smoothly in a Diels–Alder reaction³² to give adduct **81**; in this pericyclic reaction, the nitro group activates the dienophile (nitroethylene) and guides the regioselective formation of the *para*-substituted [4+2] adduct **81**. The second step (see **81** → **82**) takes advantage of the capacity of the nitro group to stabilize an adjacent negative charge; by way of a base-induced nitroaldol or Henry reaction,³³ compound **81** is joined through a carbon–carbon bond with the indicated γ,δ -unsaturated aldehyde (a polar reaction). Finally, the nitro grouping in **82** can serve as a convenient precursor to a carbon-centered radical since it is affixed to a tertiary carbon atom.³⁴ This work cleverly exploits the properties of a single functional group.³⁵

The wide variety of methods available for the synthesis of organoselenides,³⁶ and the observation that the carbon–selenium bond can be easily cleaved homolytically to give a carbon-centered radical creates interesting possibilities in organic synthesis. For example, Burke and coworkers have shown that phenylselenolactone **86** (see Scheme 16), produced by phenylselenolactonization of γ,δ -unsaturated acid **85**, can be converted to free radical intermediate **87** with triphenyltin hydride. In the presence of excess methyl acrylate, **87** is trapped stereoselectively, affording compound **88** in 70% yield;³⁷ it is noteworthy that the intermolecular carbon–carbon bond forming event takes place on the less hindered convex face of bicyclic radical **87**.



Scheme 16. Burke's two-step carbolactonization process.

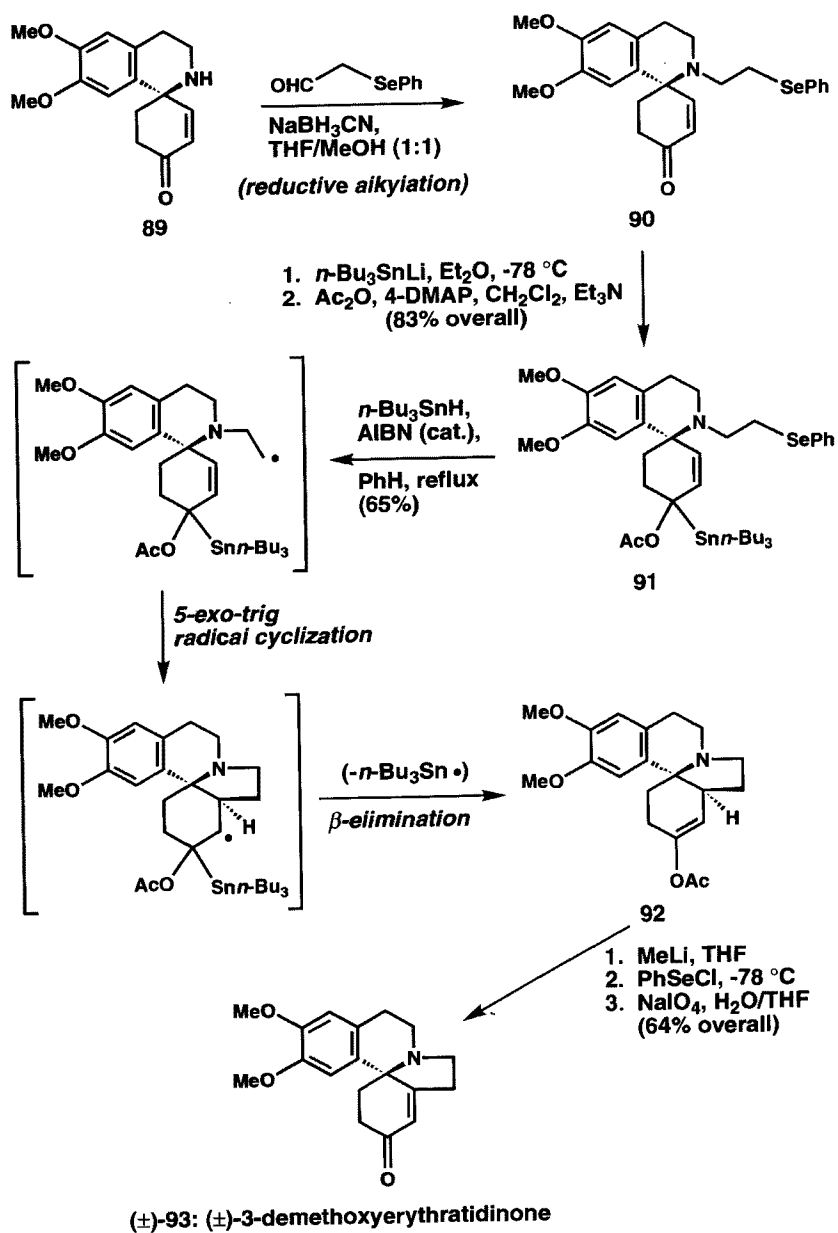


During the course of Danishefsky's elegant synthesis of the erythrina alkaloid (\pm)-3-demethoxyerythratidinone (**93**) (see Scheme 17), it was found that organoselenide **90**, prepared by reductive alkylation of amine **89**, can be converted to allylic geminal acetoxystannane **91** in two straightforward steps.³⁸ This tactic is noteworthy because radical cyclization of **91**, with concomitant fragmentation, furnishes enol acetate **92** regiospecifically, thereby allowing a controlled introduction of the requisite enone double bond in the natural product (see **92** \rightarrow (\pm)-**93**).

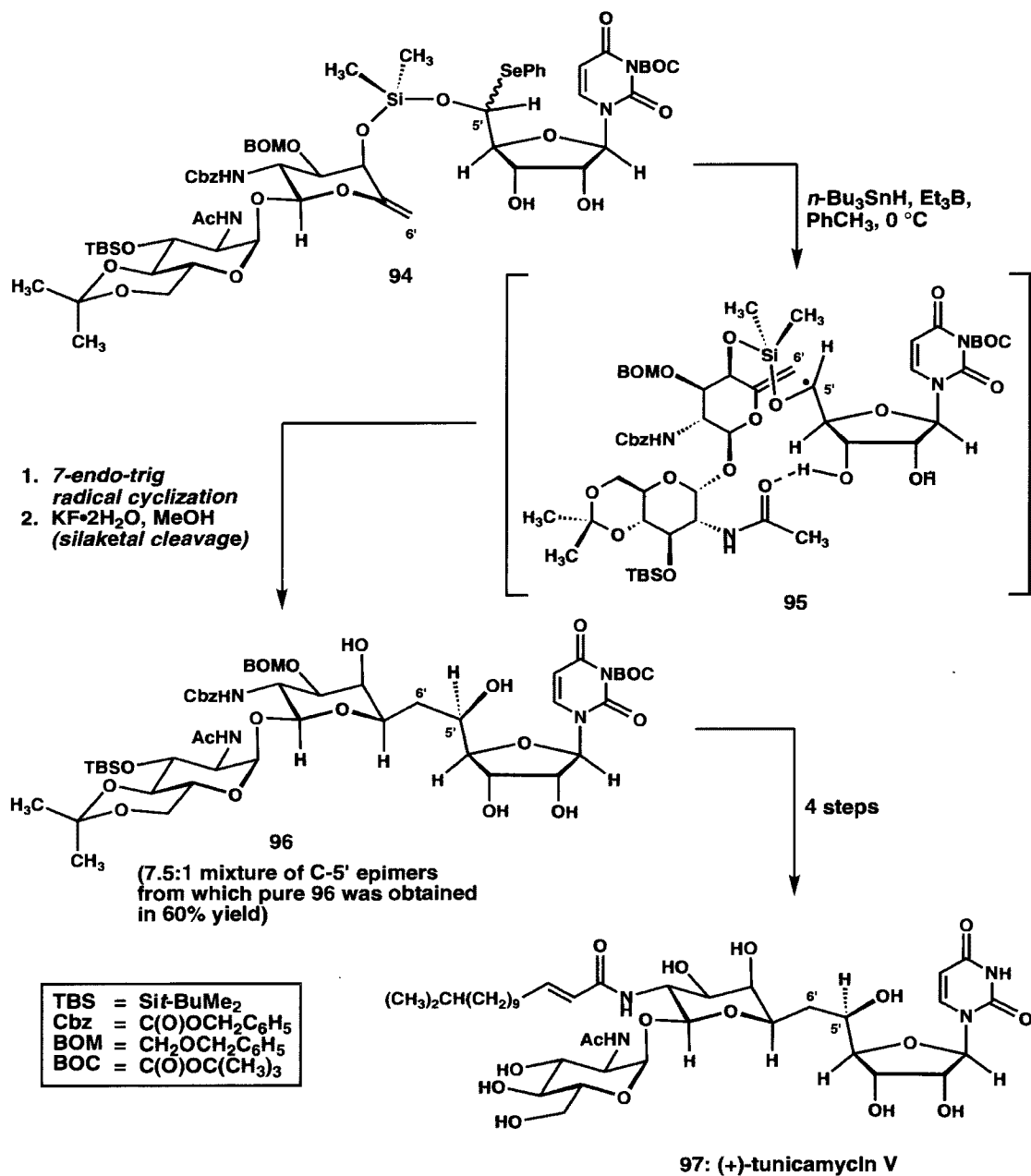
A novel organoselenide radical precursor is the key intermediate in convergent syntheses of the tunicamycin antibiotics (e.g. **97**) by A. G. Myers and his group at the California Institute of Technology (see Scheme 18).³⁹ In this elegant work, two functionalized sectors are united through a mixed-silaketel (see intermediate **94**), a group that serves as a temporary tether.⁴⁰ Homolysis of the carbon-selenium bond in **94** with tri-*n*-butyltin hydride and the low-temperature radical initiator triethylborane brings about a 7-*endo-trig* ring closure. Fluoride-induced cleavage of the silaketel then furnishes a 7.5:1 mixture of C-5' epimers in favor of **96**. This radical cyclization establishes the C5'-C6' bond and the C-5' stereocenter of the tunicamycins. The preferential formation of **96** is consistent with the hydrogen-bonded transition structure **95**. The silicon bridge brings the carbon-centered radical and the carbon-carbon double bond into proximity, and the indicated hydrogen bond stabilizes transition structure **95**; the desired configuration at C-5' emerges from this arrangement. Incidentally, if the radical cyclization of **94** is conducted in a protic solvent such as methanol, compound **96** is obtained with significantly diminished stereoselectivity (1.6:1). This observation supports the hypothesis that transition state hydrogen bonding is crucial to the desired stereochemical outcome. The total synthesis of (+)-tunicamycin V (**97**) can be achieved in four additional steps.

The reactivity of free radicals, heteroatom-centered radicals in particular, can be exploited to accomplish the formidable task of functionalizing unactivated hydrocarbons. In the early 1960s, Sir Derek Barton, a pioneer in the development of free radical reactions for use in organic synthesis, described a valuable photochemical reaction which comprises the general processes shown in Scheme 19.^{41,42} This reaction, known as the Barton reaction, is based on the premise that photolysis of nitrite ester **99**, derived from the reaction of alcohol **98** with nitrosyl chloride, furnishes a highly reactive oxygen-centered radical **100**. If such a species possesses an accessible δ -carbon-hydrogen bond, then intramolecular hydrogen atom abstraction can take place via a six-membered transition state to give a less reactive carbon-centered radical **101**. Nitrosoalcohol **102** can then be formed through the combination of **101** with the nitric oxide that was liberated in the photolysis step. It will be noted that intermediate **102** can tautomerize to oxime **103**, a convenient precursor for an aldehyde (see **103** \rightarrow **104**).

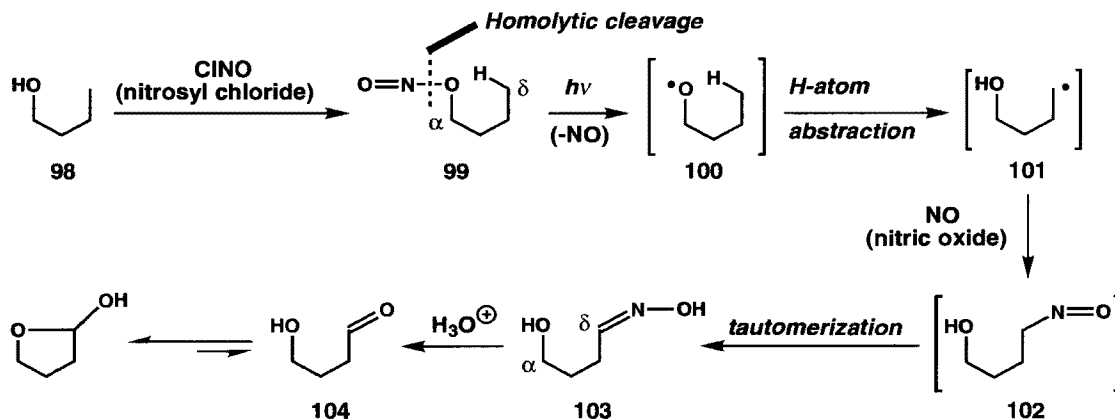
Barton devised this interesting photoinitiated method for functionalizing unactivated carbon-hydrogen bonds in response to a



Scheme 17. Danishefsky's radical addition/fragmentation process in a synthesis of (±)-3-demethoxyerythratidinone [(±)-**93**].

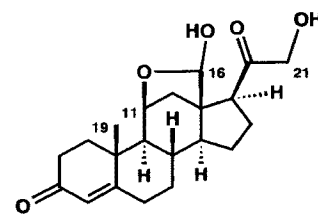


Scheme 18. Silicon-directed radical cyclization in Myers's synthesis of (+)-tunicamycin V (97).

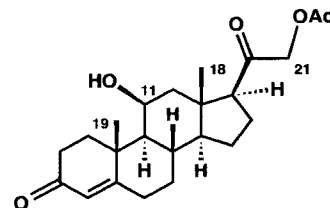


Scheme 19. Nitrite ester photolysis: the Barton reaction.

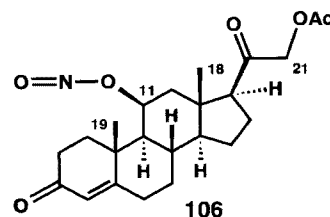
very difficult problem that emerged in the steroid field. In 1954, the structure of aldosterone (**112** see Scheme 20) was revealed as a result of the brilliant research of Reichstein and his colleagues.⁴³ A novel feature of aldosterone (**112**) is the masked aldehyde function at C-18. Although it would have been desirable to devise a feasible synthetic pathway to aldosterone starting from an abundant steroid precursor (partial synthesis), the state of the art in organic synthesis methodology at the time was not equal to the task of functionalizing an angular C-18 methyl group, a characteristic feature of many steroids. It was in this context that Barton conceived of the clever solution shown in Scheme 20. In 1960, Barton and his group reported that corticosterone acetate (**105**), a readily available steroid, can be converted to aldosterone 21-acetate (**111**) through application of the Barton reaction.⁴⁴ This interesting transformation commences with the conversion of corticosterone acetate (**105**) into the corresponding nitrite ester **106** with nitrosyl chloride in pyridine. When a solution of **106** in toluene is irradiated, alkoxy radical **107** is generated. In **107**, the oxygen-centered radical and the C-18 angular methyl group occupy neighboring regions of space, a circumstance which favors an intramolecular hydrogen atom abstraction to give carbon-centered radical **108**. The latter intermediate then captures nitric oxide (NO), the other photolysis product, furnishing a nitroso alcohol (see **109**), which finally tautomerizes to the crystalline oxime **110**. Aldosterone 21-acetate (**111**) is produced upon treatment of oxime **110** with nitrous acid [ca. 20% yield from corticosterone acetate (**105**)]. Competitive hydrogen atom abstraction from the similarly placed C-19 methyl group in **107** decreases the efficiency of the desired pathway. Although the overall yield is not high, it is noteworthy that this photoinitiated free radical reaction allowed the synthesis of approximately 60 grams of aldosterone 21-acetate (**111**), thus permitting the biological activity of this compound to be fully studied. It should be noted that an improved synthesis of



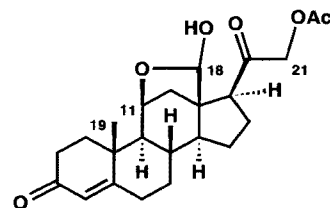
112: aldosterone



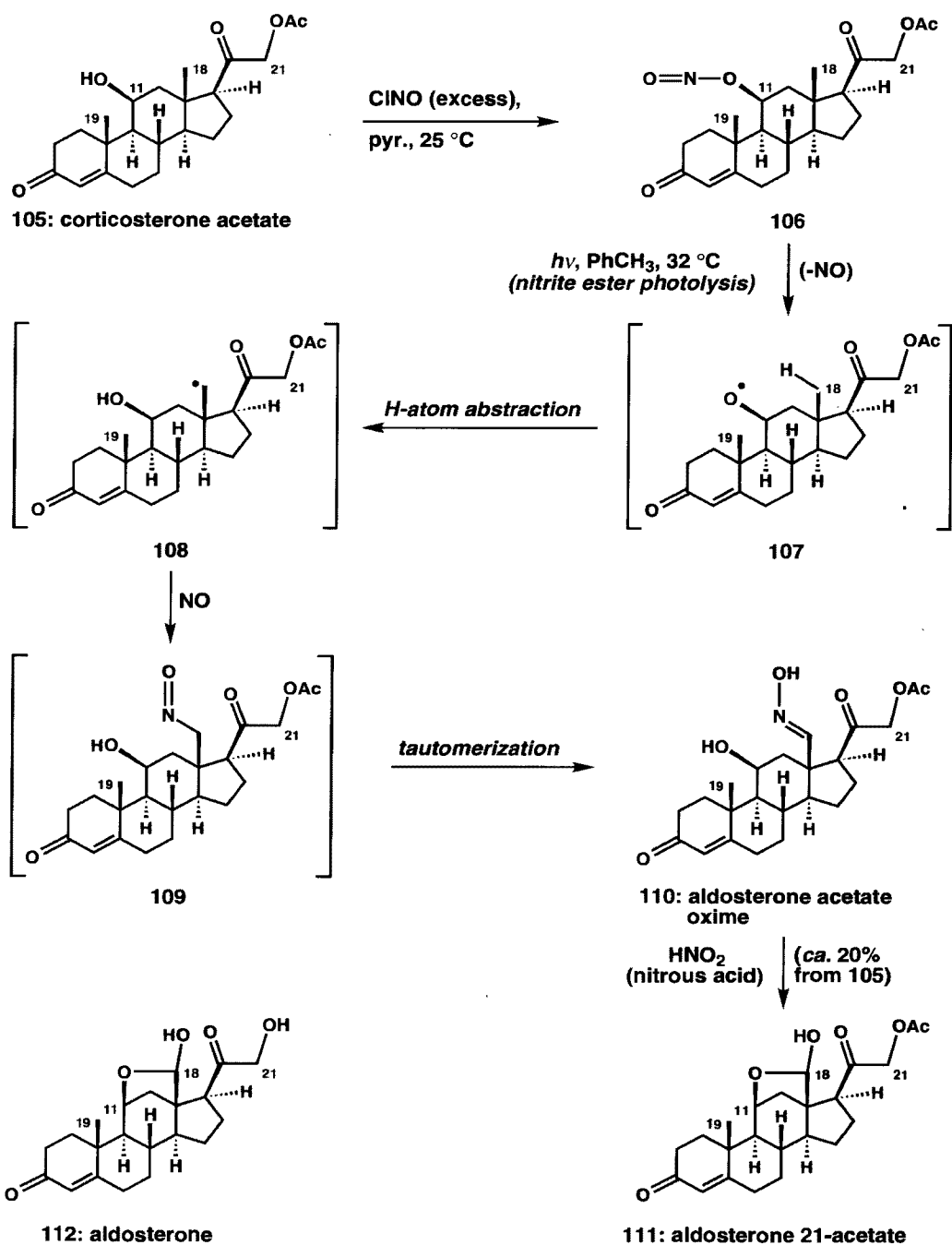
105: corticosterone acetate



106



111: aldosterone 21-acetate

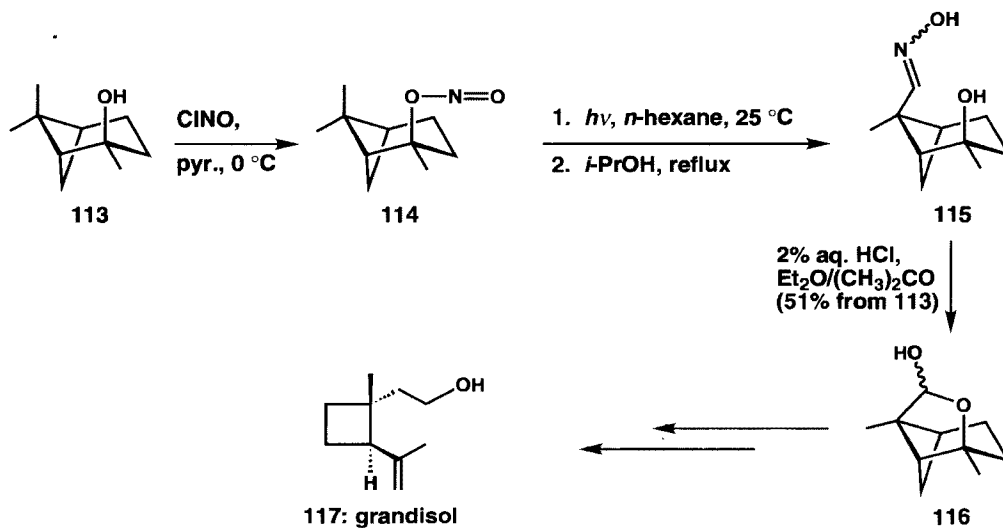
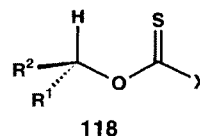


Scheme 20. The Barton synthesis of aldosterone 21-acetate (**111**).

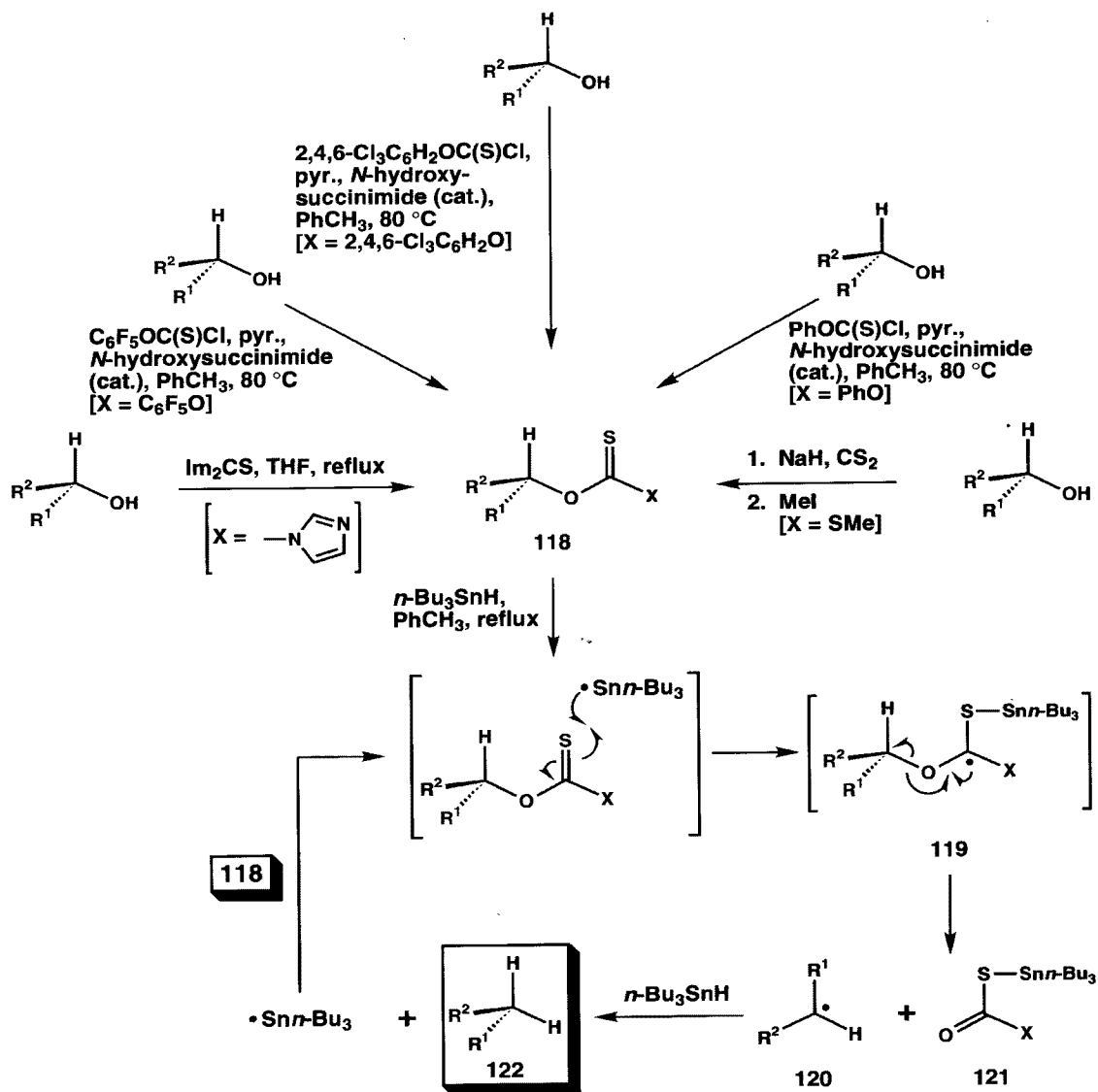
aldosterone featuring the Barton reaction was subsequently reported by Barton et al.⁴⁵

The use of the Barton reaction is not restricted to steroidal structures. For example, during the course of Magnus's total synthesis of grandisol (**117**) (see Scheme 21), it was found that alcohol **113** can be converted to lactol **116** in 51 % yield through the application of Barton's nitrite photolysis method (see **113** → **114** → **115** → **116**, Scheme 21).^{46,47} A good substrate for a Barton reaction is one having a rigid framework with a carbon–hydrogen bond situated in proximity to an oxygen radical precursor (e.g. a nitrite ester); hydrogen atom abstraction occurs via a six-center transition state.

The affinity of a trialkyltin radical for the sulfur atom of a thiocarbonyl forms the basis of a particularly useful reaction in organic synthesis: the Barton–McCombie reaction (see Scheme 22).^{48,49} In two steps, the Barton–McCombie reaction accomplishes the replacement of the hydroxyl group of an alcohol with a hydrogen, a functional group transformation of immense importance in organic synthesis. The popularity of this method derives from the facility with which secondary alcohols, even hindered secondary alcohols, can be deoxygenated. Scheme 22 illustrates the key features of the Barton–McCombie reaction. The first step is the production of a thioester **118** through thioacylation of an alcohol with a suitable thiocarbonyl compound; a virtue of the Barton–McCombie reaction is that a variety of thioesters can be utilized.⁵⁰ In the second step, **118** is exposed to tri-*n*-butyltin hydride in refluxing toluene (xylene or *para*-cymene can also be used). Tri-*n*-butyltin radical, generated *in situ*, selectively attacks the thiocarbonyl sulfur atom of **118**,



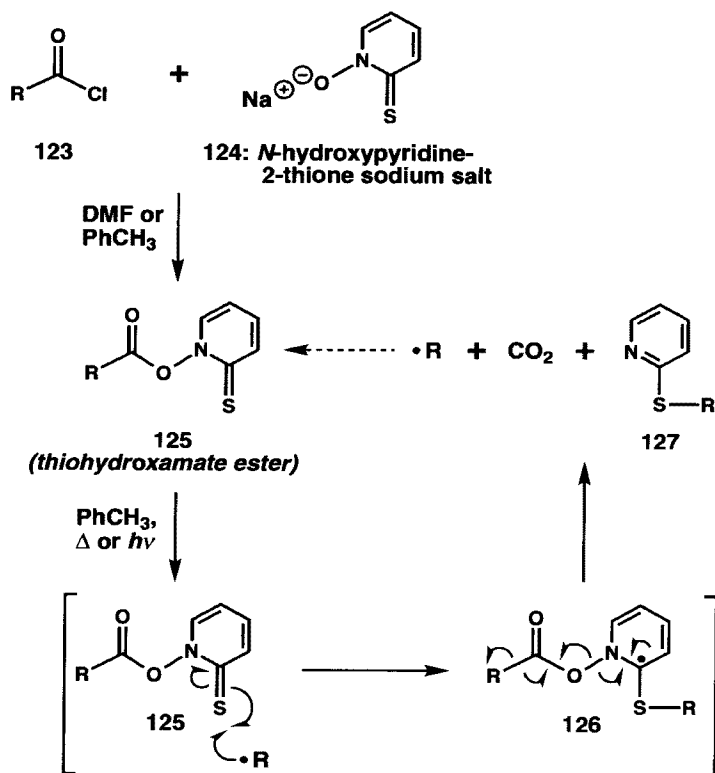
Scheme 21. The Barton reaction in Magnus's synthesis of grandisol (**117**).



Scheme 22. The Barton-McCombie reaction [$\text{R}^1\text{R}^2\text{CHOH} \rightarrow \text{R}^1\text{R}^2\text{CH}_2$].

affording radical **119** which dissociates into two fragments, radical intermediate **120** and carbonyl compound **121**. Finally, carbon radical **120** abstracts a hydrogen atom from tri-*n*-butyltin hydride to give the reduced product **122** and *n*-Bu₃Sn[•]. The affinity of the tin radical for the thiocarbonyl sulfur atom in **118**, the overall conversion of a carbon–sulfur double bond to a stronger carbon–oxygen double bond, and the increase in entropy resulting from the dissociation of the intermediate radical **119** into two fragments are all driving forces for this valuable reaction.

In more recent studies, the Barton group has shown that *O*-acyl thiohydroxamates (thiohydroxamate esters) are convenient sources of alkyl radicals.^{49c,51,52} Barton's thiohydroxamate ester chemistry is mild and easily executed, and the intermediate organic radicals are amenable to a wide variety of useful transformations. A thiohydroxamate ester of the type **125** (see Scheme 23) can be formed

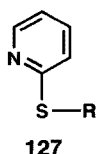


Thermodynamic driving forces-

- enthalpic:** 1. conversion of a thiocarbonyl to a stronger carbonyl (CO₂);
2. aromatization of the pyridine nucleus

- entropic:** 1. production of three product molecules from one substrate molecule (125)

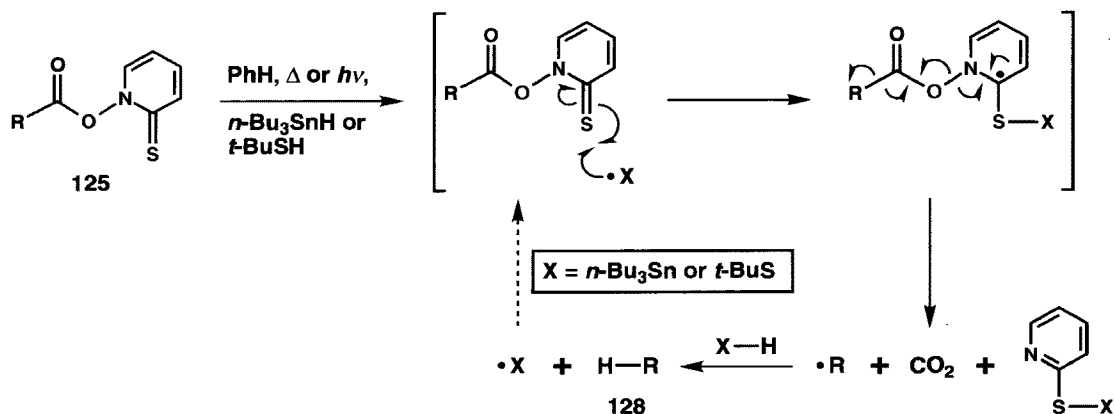
Scheme 23. Barton's thiohydroxamate ester chemistry: synthesis of alkyl pyridyl sulfides (**127**).



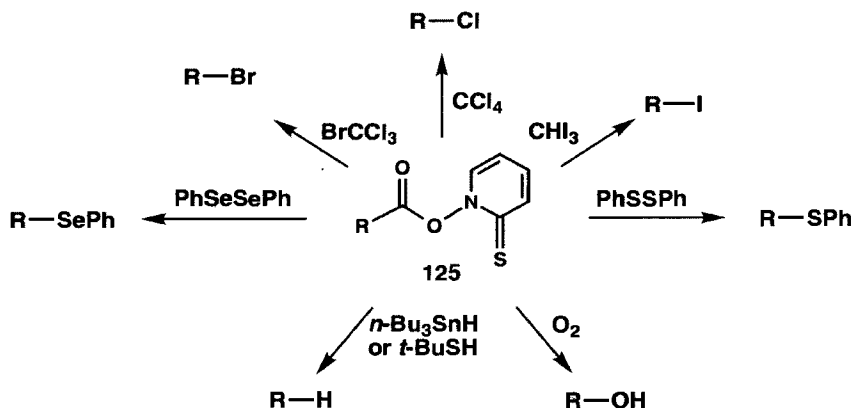
from the reaction of an activated carboxylic acid derivative, such as acid chloride **123**, with the commercially available sodium salt of *N*-hydroxypyridine-2-thione (**124**). If a solution of **125** in toluene is simply heated to reflux or irradiated with a tungsten lamp, an alkyl pyridyl sulfide of the type **127** can be produced in excellent yields. In this transformation, an alkyl radical (R^\bullet) formed by thermolytic or photolytic decomposition of thiohydroxamate ester **125** attacks the thiocarbonyl sulfur atom of **125** to give a new radical intermediate **126**. Concerted or stepwise fragmentation of **126** then results in the formation of CO_2 , the alkylpyridyl sulfide **127**, and an alkyl radical (R^\bullet) which is available for reaction with another molecule of **125**. The formation of a strong carbon-oxygen π bond (CO_2) in exchange for a weaker carbon-sulfur π bond, and aromatization to the pyridine nucleus (**127**) provide powerful enthalpic driving forces for this fragmentation. The reaction is also favored entropically because three entities are formed from one substrate molecule.

If the reaction just described is conducted in the presence of a suitable hydrogen atom donor such as tri-*n*-butyltin hydride or *tert*-butyl hydrosulfide, reductive decarboxylation occurs via a radical chain mechanism to give an alkane (see **125** \rightarrow **128**, Scheme 24). Carboxylic acids can thus be decarboxylated through the intermediacy of their corresponding thiohydroxamate esters in two easily executed steps. In this reductive process, one carbon atom, the carbonyl carbon, is smoothly excised.

The scope of Barton's thiohydroxamate ester chemistry has been significantly expanded by the finding that the intermediate alkyl radicals (R^\bullet) can be intercepted by a host of neutral molecules (see Scheme 25).^{42b,49c,52,53} Several different classes of compounds can thus be prepared from a common thiohydroxamate ester precursor.



Scheme 24. Barton's thiohydroxamate ester chemistry: reductive decarboxylation.

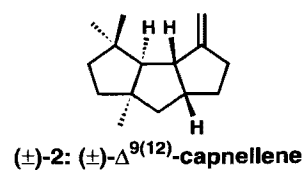
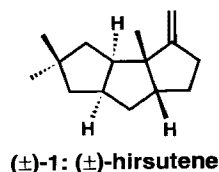
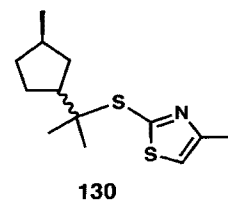
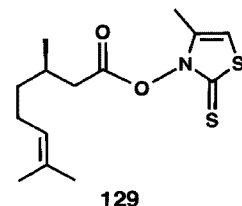


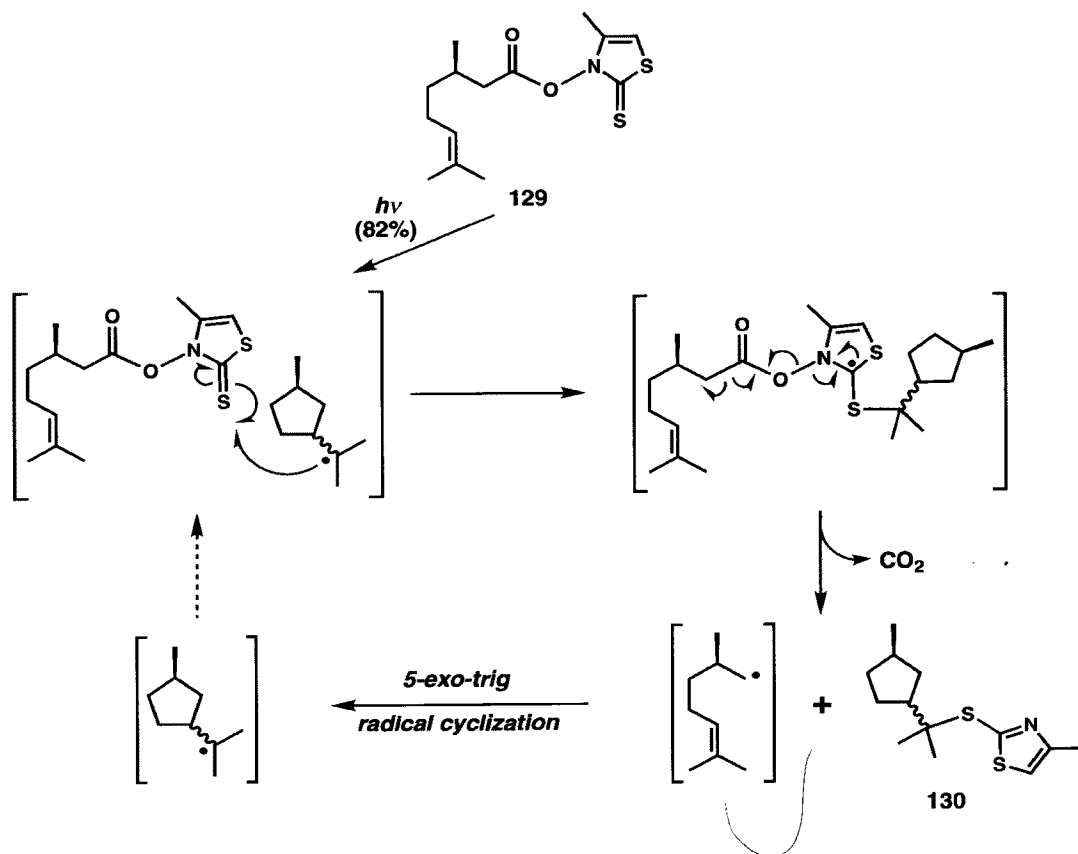
Scheme 25. Barton's thiohydroxamate ester chemistry: use of neutral molecule radical traps.

Carbon-centered radicals generated by Barton's thiohydroxamate method can also participate in ring-forming reactions (see Scheme 26).^{52b,53} For example, irradiation of **129** results in the formation of compound **130** (82% yield). The outcome of this transformation is reminiscent of Stork's elegant radical cyclization/trapping processes (see Schemes 7 and 8), in that both alkene carbon atoms have become functionalized.

On the basis of the examples addressed thus far, it is clear that radical reactions can accomplish manifold transformations in organic synthesis. One of the outstanding achievements of synthetic radical chemistry is the development of synthetic strategies based on controlled, tandem radical cyclizations. The efficiency of such strategies is exemplified in the substantial and elegant synthetic work of D.P. Curran and his group.⁵⁴ The remainder of this chapter will address the concise total syntheses of (\pm)-hirsutene [(\pm)-**1**]⁵⁵ and (\pm)- $\Delta^{9(12)}$ -capnellene [(\pm)-**2**]⁵⁶ by the Curran group.

A relatively large class of natural products is distinguished by a fusion of three cyclopentane rings. These tricyclopentanoid or triquinane natural products derive from various sources and are classified according to ring fusion as linear, angular, or propellane (see Figure 1 for representative examples). Triquinane natural products, many of which possess significant antibiotic and/or antitumor activity, occupy an important place in organic synthesis, for they have stimulated the development of numerous methods for the construction of condensed cyclopentanoids.⁵⁷ Although synthetic strategies that construct each ring of the tricyclic framework in a stepwise fashion have proven successful, those that employ tandem radical cyclizations are particularly powerful because they can accomplish the formation of more than one ring in a single step. As shown by D.P. Curran and his group, tandem radical or radical-initiated polyolefinic cyclizations are ideally suited for the synthesis of triqui-





Scheme 26. Barton's thiohydroxamate ester chemistry: construction of a carbon–carbon bond.

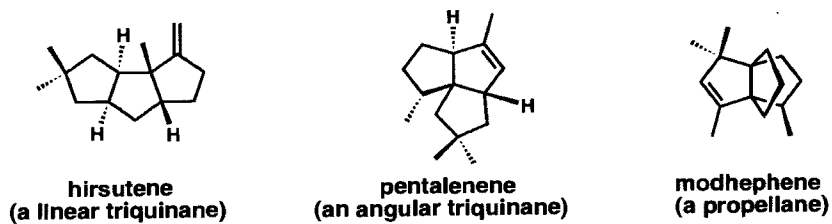


Figure 1. Representative linear, angular, and propellane triquinane natural products.

nane natural products. In the sections below, the details of the synthesis of (\pm)-hirsutene [(\pm)-**1**] and (\pm)- $\Delta^{9(12)}$ -capnellene [(\pm)-**2**] by Curran et al. are described.

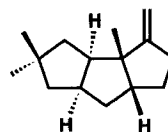
23.2 Retrosynthetic Analysis and Strategy

Hirsutene (**1**) and $\Delta^{9(12)}$ -capnellene (**2**), the parent members of the hirsutane and capnellane families of triquinane natural products, respectively, are isomeric molecules that possess four contiguous stereogenic centers, one of which is quaternary. The linearly fused tricyclopentanoid frameworks of compounds **1** and **2** are obviously very similar, differing only with respect to the positions of the three methyl groups. An asset of Curran's tandem radical cyclization strategy is that it provides a unified entry into a wide variety of linear condensed cyclopentanoid natural products. As a result, it is possible to devise nearly identical retrosynthetic pathways for these structurally related molecules.

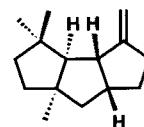
The key features of Curran's productive and elegant tandem radical cyclization strategy are illustrated in a retrosynthetic analysis for hirsutene (**1**) (see Scheme 27). The final synthetic event was projected to be an intermolecular transfer of a hydrogen atom from tri-*n*-butyltin hydride to the transitory tricyclic vinyl radical **131**. The latter can then be traced to bicyclic tertiary radical **132** and thence to monocyclic primary radical **133** through successive hex-5-enyl-like radical cyclizations. It was anticipated that the initial radical **133** could be generated through the abstraction of the iodine atom from **134** by tri-*n*-butyltin radical. According to this strategy, primary iodide **134**, a rather simple *trans*-disubstituted cyclopentene could be transformed directly into hirsutene by a radical-initiated tandem bicyclization process and a terminating hydrogen atom transfer. Two carbon-carbon bonds, two contiguous stereogenic centers, and two carbocyclic rings would be formed in this elegant transformation.

It is important to note here that both of the 5-*exo* radical cyclizations (**133** \rightarrow **132** \rightarrow **131**, Scheme 27) must proceed in a *cis* fashion; the transition state leading to a strained *trans*-fused bicyclo[3.3.0]octane does not permit efficient overlap between the singly occupied molecular orbital (SOMO) of the radical and the lowest unoccupied molecular orbital (LUMO) of the alkene. The relative orientation of the two side chains in the monocyclic radical precursor **134** is thus very significant because it dictates the relationship between the two outer rings (i.e. *syn* or *anti*) in the tricyclic product. The *cis-anti-cis* ring fusion stereochemistry of hirsutene would arise naturally from a cyclization precursor with *trans*-disposed side chain appendages (see **134**).

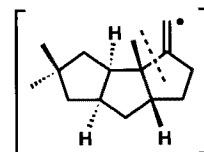
trans-Disubstituted cyclopentene **134**, the projected radical precursor, can be traced retrosynthetically to organometallic reagent **135** and *cis*-fused bicyclic lactone **136**. In the synthetic direction,



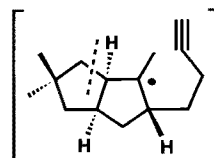
1: hirsutene



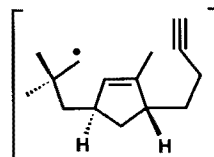
2: $\Delta^{9(12)}$ -capnellene



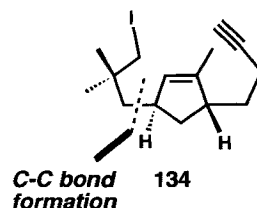
131



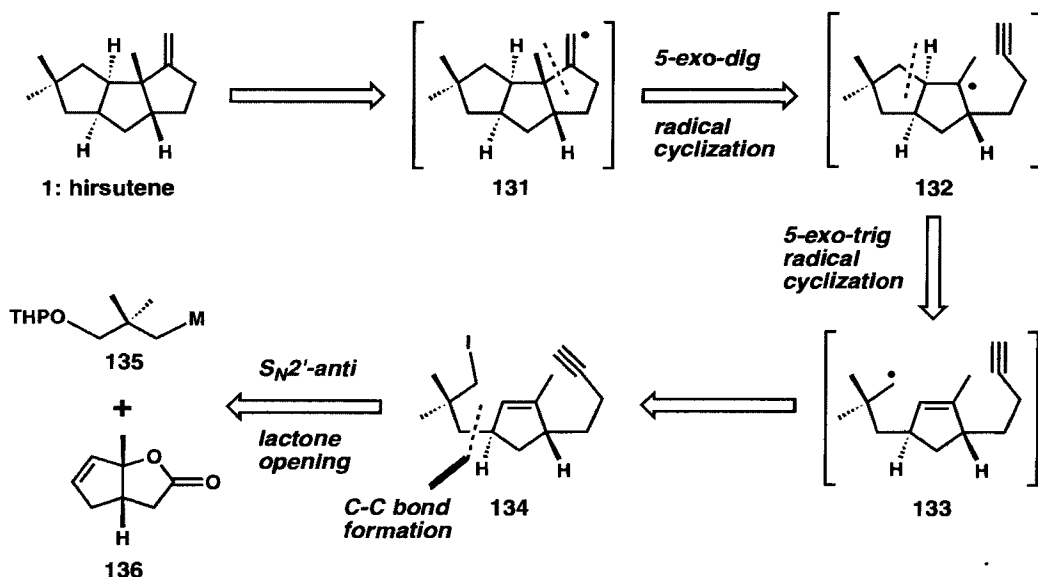
132



133



C-C bond formation 134

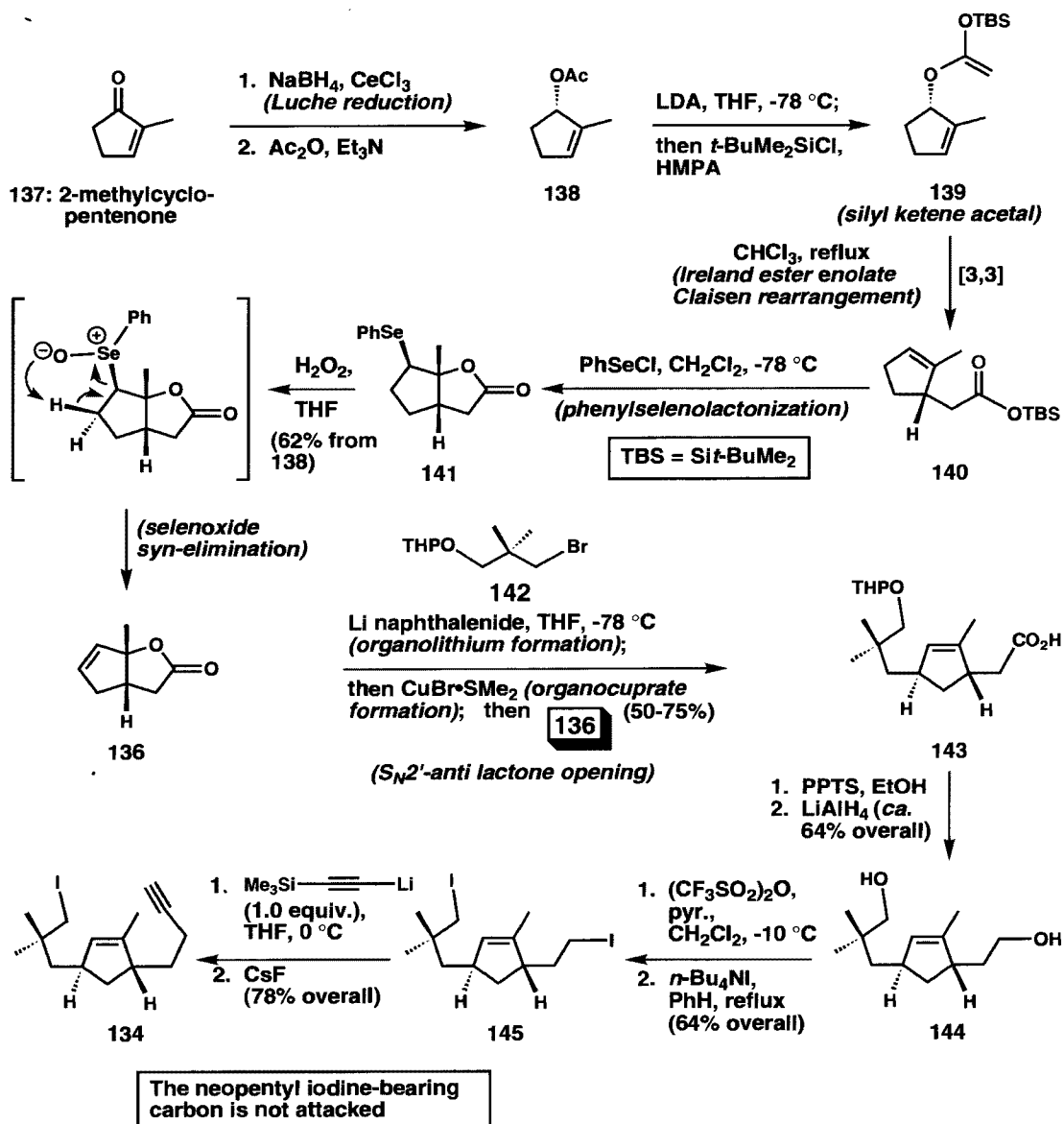


Scheme 27. Retrosynthetic analysis of hirsutene (**1**).

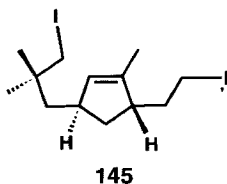
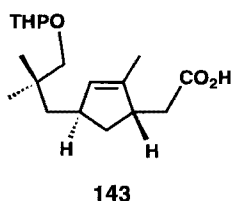
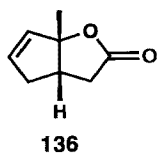
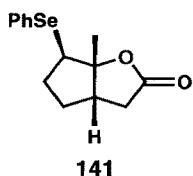
introduction of the left-hand side chain **135** by S_N2' -anti opening of vinyl lactone **136**, followed by standard manipulations, could furnish the penultimate intermediate **134**. The left-hand side chain in **134** possesses the initiating terminus for the tandem radical cyclization, while the terminal alkyne in the right-hand side chain constitutes the cascade terminator. The execution of Curran's total synthesis of (\pm)-hirsutene [(\pm)-**1**] and (\pm)- $\Delta^{9(12)}$ -capnellene [(\pm)-**2**] based on this strategy is described below.

23.3 Total Synthesis

Schemes 28 and 29 illustrate Curran's synthesis of (\pm)-hirsutene [(\pm)-**1**]. Luche reduction⁵⁸ of 2-methylcyclopentenone (**137**), followed by acetylation of the resulting allylic alcohol, furnishes allylic acetate **138**. Although only one allylic acetate stereoisomer is illustrated in Scheme 28, compound **138** is, of course, produced in racemic form. By way of the powerful Ireland ester enolate Claisen rearrangement,⁵⁹ compound **138** can be transformed to γ,δ -unsaturated *tert*-butyldimethylsilyl ester **140** via the silyl ketene acetal intermediate **139**. In **140**, the silyl ester function and the methyl-substituted ring double bond occupy neighboring regions of space, a circumstance that favors a phenylselenolactonization reac-



Scheme 28. Curran's synthesis of (±)-hirsutene [(±)-1]: construction of intermediate 134.

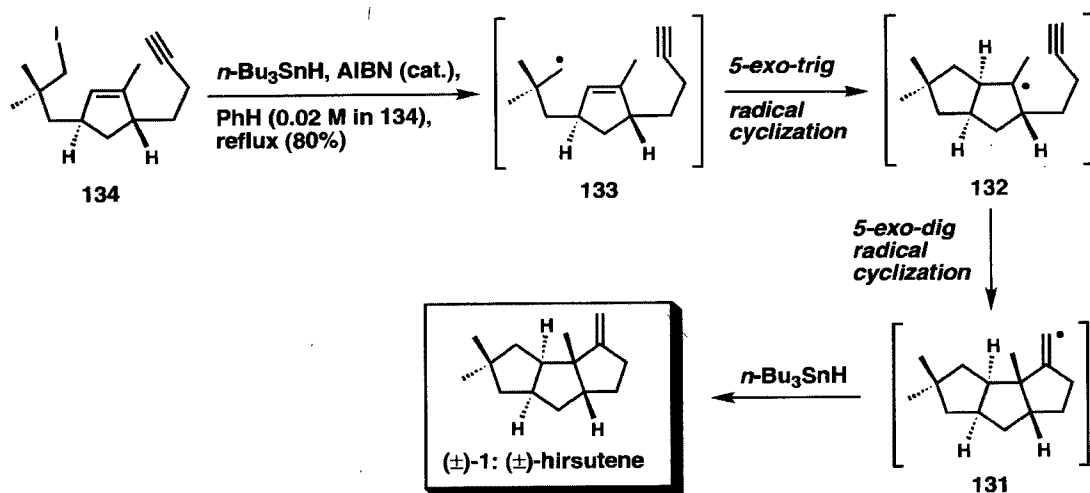


tion to give bicyclic lactone **141**. In practice, unsaturated silyl ester **140** is converted directly to **141** with phenylselenenyl chloride.³⁶ Oxidation of selenide **141** to the corresponding selenoxide by hydrogen peroxide with concomitant *syn* elimination provides vinyl lactone **136** (62 % overall yield from allylic acetate **138**).

After considerable experimentation, it was found that the action of two equivalents of lithium naphthalenide on neopentyl bromide **142** in cold (-78°C) THF produces, through reductive lithiation, the corresponding organolithium reagent. Sequential treatment of the latter species with $\text{CuBr}\cdot\text{SMe}_2$ complex and vinyl lactone **136** then affords carboxylic acid **143** in variable yields ranging from 50 to 75 %. It is noteworthy that **143** is produced as a single regio- and stereoisomer. The *in situ* generated organocuprate reagent reacts with the less hindered convex face of **136** in the $\text{S}_{\text{N}}2'$ lactone opening.⁶⁰ This crucial transformation creates a key carbon-carbon bond, introduces necessary functionality, and establishes the requisite *trans* relationship between the left- and right-hand side chains.

From *trans*-3,5-disubstituted cyclopentene **143**, the pivotal tandem radical cyclization precursor **134** can be constructed in straightforward fashion. After acid-catalyzed solvolysis of the THP ether in **143**, lithium aluminum hydride reduction of the carboxyl terminus affords diol **144** in ca. 64 % overall yield. When the latter is exposed to several equivalents of trifluoromethanesulfonic (triflic) anhydride and pyridine in CH_2Cl_2 at -10°C , a ditriflate is produced. When a solution of this substance in benzene is treated with excess tetra-*n*-butylammonium iodide and heated to reflux, diiodide **145** is formed in 64 % overall yield. Although both iodine-bearing carbons in **145** could conceivably undergo nucleophilic attack in the presence of a reactive nucleophile, the neopentyl iodine-bearing carbon is considerably more hindered than the other. Consequently, the prospects for effecting a selective displacement of the less hindered iodide with an acetylide nucleophile seemed very favorable. Indeed, exposure of a solution of diiodide **145** in THF at 0°C to lithium trimethylsilylacetylide (1 equiv.), followed by removal of the trimethylsilyl group with fluoride ion, furnishes key intermediate **134** (78 % overall yield). As expected, only the non-neopentyl primary iodide is displaced.

The stage is now set for the tandem radical bicyclization event. Remarkably, when a solution of iodide **134** in benzene (0.02 M) is treated with tri-*n*-butyltin hydride (1.3 equiv.) and a catalytic amount of AIBN and heated to reflux for 1 h, (\pm)-hirsutene [(\pm)-**1**] is produced in ca. 80 % yield (see Scheme 29). In this transformation, tri-*n*-butyltin radical, generated *in situ*, reacts with iodide **134** to give the putative primary radical **133**. The intermediacy of **133** is brief, for it participates in a facile 5-*exo-trig* radical cyclization to give a new carbon-centered radical **132**. With an effective alkyne radical acceptor only five atoms removed, **132** takes part in a 5-*exo-dig* radical cyclization to give the reactive tricyclic vinyl radical **131**; the action of tri-*n*-butyltin radical on iodide **134** brings about successive chain-to-ring and ring-to-chain cyclizations to



Scheme 29. Synthesis of (±)-hirsutene [(±)-1] by tandem radical cyclizations.

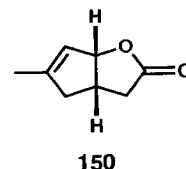
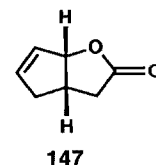
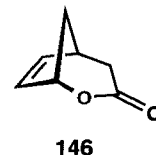
give **131**. Finally, abstraction of a hydrogen atom from tri-*n*-butyltin hydride affords (±)-hirsutene [(±)-1] and regenerates tri-*n*-butyltin radical. As expected, both 5-*exo* radical cyclizations proceed in a *cis* fashion. The *cis*-*anti*-*cis*-stereochemistry present in hirsutene thus arises naturally from the *trans*-3,5-disubstituted cyclopentene radical precursor. It should also be noted that although tertiary radicals are more stable than vinyl radicals, the 5-*exo*-dig cyclization of **132** is still exothermic and fast, because a carbon-carbon σ bond is formed at the expense of a weaker carbon-carbon π bond.

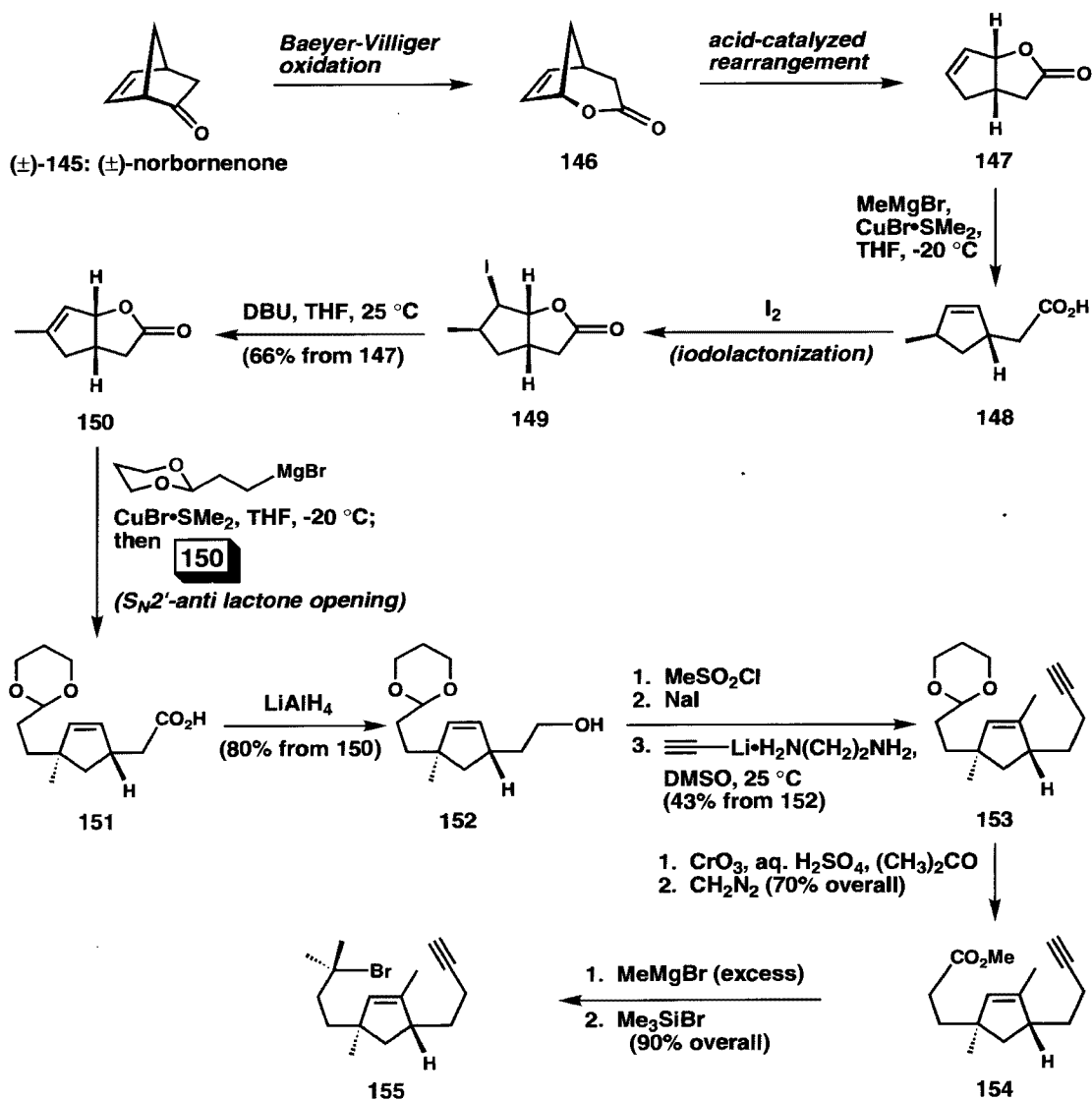
Curran's synthesis of (±)- $\Delta^{9(12)}$ -capnellene [(±)-2] is detailed in Schemes 30 and 31. This synthesis commences with the preparation of racemic bicyclic vinyl lactone **147** from (±)-norbornenone [(±)-**145**] by a well-known route.⁶¹ Thus, Baeyer-Villiger oxidation of (±)-**145** provides unsaturated bicyclic lactone **146**, a compound that can be converted to the isomeric fused bicyclic lactone **147** by acid-catalyzed rearrangement. Reaction of **147** with methylmagnesium bromide/CuBr•SMe₂ in THF at -20 °C takes the desired course and affords unsaturated carboxylic acid **148** in nearly quantitative yield. Iodolactonization of **148** to **149**, followed by base-induced elimination, then provides the methyl-substituted bicyclic vinyl lactone **150** as a single regioisomer in 66% overall yield from **147**.

Although the methyl-bearing sp²-hybridized carbon in **150** is more hindered than the corresponding carbon in **136** (see Scheme 28), **150** participates in a regio- and stereoselective S_N2'-*anti* lactone opening reaction with the organocuprate reagent formed from the indicated Grignard reagent and CuBr•SMe₂.^{62,63} This S_N2' addition accomplishes the introduction of the left-hand side chain and the requisite quaternary stereocenter. The desired unsaturated

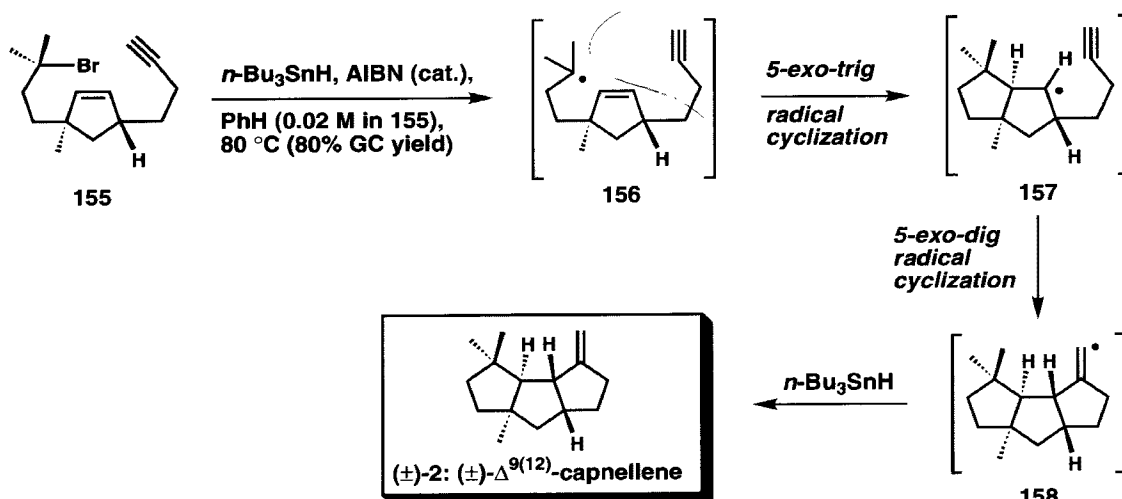


(±)-**145**: (±)-norbornenone





Scheme 30. Curran's synthesis of (±)- $\Delta^{9(12)}$ -capnellene [(±)-2]: construction of intermediate **155**.

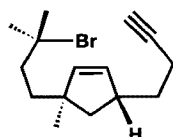
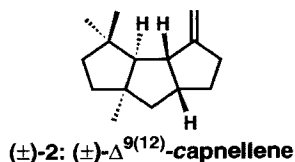


Scheme 31. Synthesis (±)- $\Delta^{9(12)}$ -capnellene [(±)-2] by tandem radical cyclizations.

carboxylic acid **151** is obtained in high yield together with a small amount (ca. 10%) of a regioisomeric substance produced by nucleophilic attack at the carbon bearing the lactone ring oxygen ($\text{S}_{\text{N}}2$ opening). To facilitate isolation, the crude mixture of regioisomeric acids was directly reduced with lithium aluminum hydride and the resulting alcohols were separated chromatographically. In this way, the desired alcohol **152** can be obtained in 80% yield from vinyl lactone **150**.

From **152**, the synthesis of the tandem radical cyclization precursor **155** only requires a few manipulations of the two side chains. To this end, treatment of primary alcohol **152** with methanesulfonyl chloride, followed by displacement of the resulting mesylate with iodide ion, provides the corresponding primary iodide. Reaction of the latter substance with lithium acetylide/ethylene diamine complex in DMSO at 25 °C then furnishes alkyne **153** in 43% yield from **152**. Under the conditions of a Jones oxidation, the dioxane acetal is hydrolyzed and the resulting aldehyde is oxidized to the corresponding carboxylic acid. Esterification of the newly formed carboxyl group with diazomethane (CH_2N_2) then gives methyl ester **154** in 70% overall yield. In the presence of excess methylmagnesium bromide, **154** undergoes conversion to a tertiary alcohol that can subsequently be converted to tertiary bromide **155** with trimethylsilyl bromide (90% overall yield). Since compound **155** was difficult to purify by chromatography, it was used in the next step in crude form.

A most attractive feature of radical reactions that recommends their use in the synthesis of complex molecules is that steric crowding, particularly on the radical center, is tolerated in many instances. Indeed, radical reactions are ideally suited for the con-

**155**

struction of crowded carbon–carbon bonds because radical intermediates, in contrast to organometallic species, are not encumbered with counterions or aggregation spheres.^{3d} Carbon-centered radicals are also highly reactive intermediates that add to carbon–carbon π bonds via early, reactant-like transition states. It is, therefore, not surprising that compound **155** undergoes conversion to $(\pm)\text{-}\Delta^{9(12)}$ -capnellene **[(±)-2]** on treatment with tri-*n*-butyltin hydride (1.2 equiv.) and AIBN (catalytic amount) in benzene at 80 °C. $(\pm)\text{-}\Delta^{9(12)}$ -Capnellene **[(±)-2]** is produced in 61% yield (80% GC yield), and is the only tricyclic substance observed. It is presumed that reduction of the carbon–bromine bond in **155** with tri-*n*-butyltin radical generates a transient tertiary radical that undergoes conversion to **(±)-2** through successive 5-*exo* radical cyclizations (**156** → **157** → **158**).

23.4 Conclusion

Fundamental research in physical organic chemistry uncovered many of the characteristics of radical reactions and stimulated impressive advances in organic synthesis in the 1980s. In this chapter, an attempt has been made to highlight some of the features of radical reactions that make them ideally suited for applications in organic synthesis. Through the application of radical chemistry, valuable functional group transformations and challenging carbon–carbon bond constructions can be achieved under unusually mild reaction conditions. The elegant contributions of D. P. Curran and others demonstrate that a prudent sequence of elementary radical reactions can create powerful, one-pot strategies for the synthesis of complex polycyclic molecules. Indeed, tandem or sequential radical cyclizations can offer exceedingly concise solutions to challenging problems in organic synthesis.⁶⁴

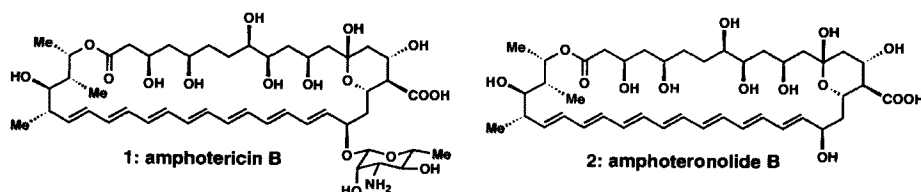
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C



K. C. Nicolaou (1987)

Amphoteronolide B and Amphotericin B

24.1 Introduction

Amphotericin B (**1**) and amphoteronolide B (**2**) are amongst the most prominent members of the clinically important polyene macrolide¹ family of natural products. Named for their large macrolactone ring and conjugated all-*trans* polyolefinic region, the polyene macrolides comprise one of the most intriguing and challenging areas of natural products chemistry. Amphotericin B (**1**),² a widely used antifungal agent, is produced by *Streptomyces nodosus* and remains the only member of the polyene macrolides whose structure has been established by X-ray crystallographic analysis.³

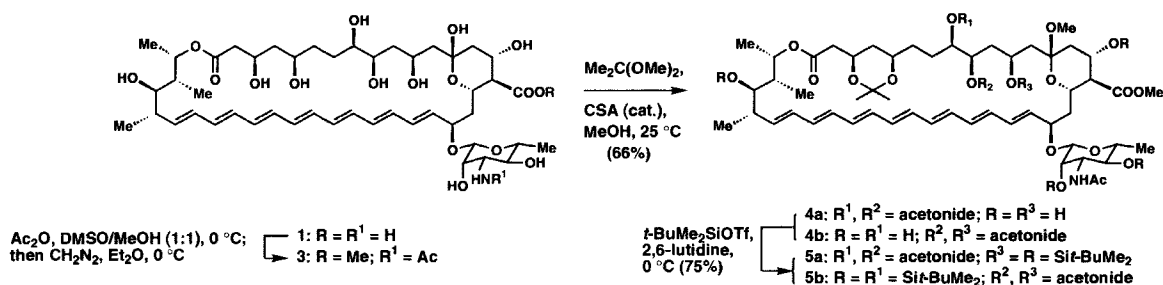
With its seven contiguous *trans* double bonds, macrolactone ring, numerous stereogenic centers and β -glycoside, amphotericin B (**1**) and its aglycon (**2**) presented a serious challenge to the state of the art of asymmetric synthesis and acyclic stereocontrol. Thus the Nicolaou group embarked in the early 1980s on a program directed towards the total synthesis of these formidable targets. In order to acquire a more intimate familiarity with the chemistry of amphotericin B (**1**) and to facilitate the final stages of a projected total synthesis, studies were first undertaken which included the derivatization and degradation of amphotericin B (**1**)⁴ and the preparation of its aglycon, amphoteronolide B (**2**).⁵

24.1.1 Degradation Studies

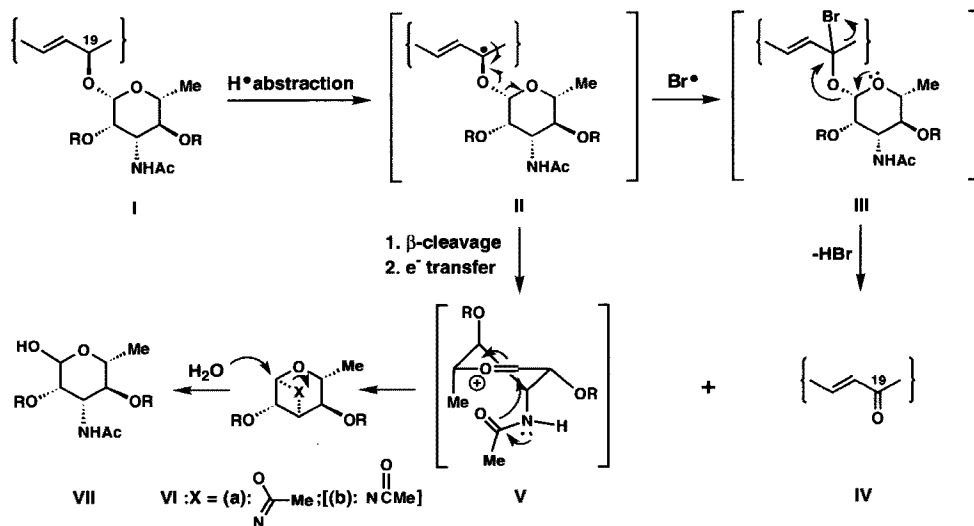
The insolubility of amphotericin B (**1**) in common organic solvents necessitated the preparation of tractable intermediates that were more

amenable to chromatographic purification and spectroscopic identification. Previous studies⁶ had shown that selective acetylation of the amino group, followed by methylation of the carboxylic acid function, results in the formation of *N*-acetyl amphotericin B methyl ester (**3**, Scheme 1), a derivative with improved physical properties over **1**. Further protection and differentiation of the various hydroxyl groups was sought. The first breakthrough was recorded when exposure of derivative **3** (Scheme 1) to $\text{Me}_2\text{C}(\text{OMe})_2$ and a catalytic amount of camphorsulfonic acid (CSA) in methanol produced diacetoneides **4ab** in 66 % yield (1:1 to 5:1 ratio, depending on reaction time). Persilylation of **4ab** with *tert*-BuMe₂SiOTf in the presence of 2,6-lutidine furnishes the pentasilyl ether derivatives **5ab** in 75 % yield (ca. 3:1 ratio). Having established this important key intermediate (**5ab**), it was then decided to devise a method for deglycosidation of amphotericin B (**1**) to enable the exploration of the chemistry of amphoteronolide B (**2**) and other projected key intermediates.

Conventional methods of deglycosidation, when applied to amphotericin B (**1**), failed to produce the intact aglycon owing to the high stability of the aminosugar, and to the high sensitivity of the aglycon towards strongly acidic conditions. In order to circumvent these difficulties, a new method for deglycosidation applicable to amphotericin B (**1**) was devised based on oxidative removal of the carbohydrate unit under neutral conditions. Scheme 2 outlines the mechanistic rationale upon which this novel reaction is based. It was anticipated that the polyolefinic system of an amphotericin B derivative would permit radical formation at C-19 by hydrogen atom abstraction under appropriate conditions (e.g. *N*-bromosuccinimide homolysis). The radical thus formed (**II**) could then proceed to the labile bromo derivative **III**, or directly collapse via β -cleavage to form enone **IV** and a mycosaminyl radical, which would lead to the oxonium species **V** upon electron transfer/oxidation. These same species **IV** and **V** would also be expected to result from collapse of bromide **III** with participation by the ring oxygen as shown in Scheme 2. The highly reactive oxonium species **V** could then



Scheme 1. Protection of amphotericin B (**1**).

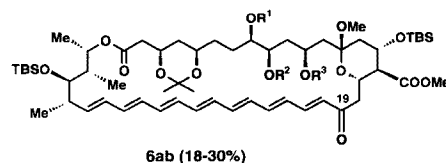


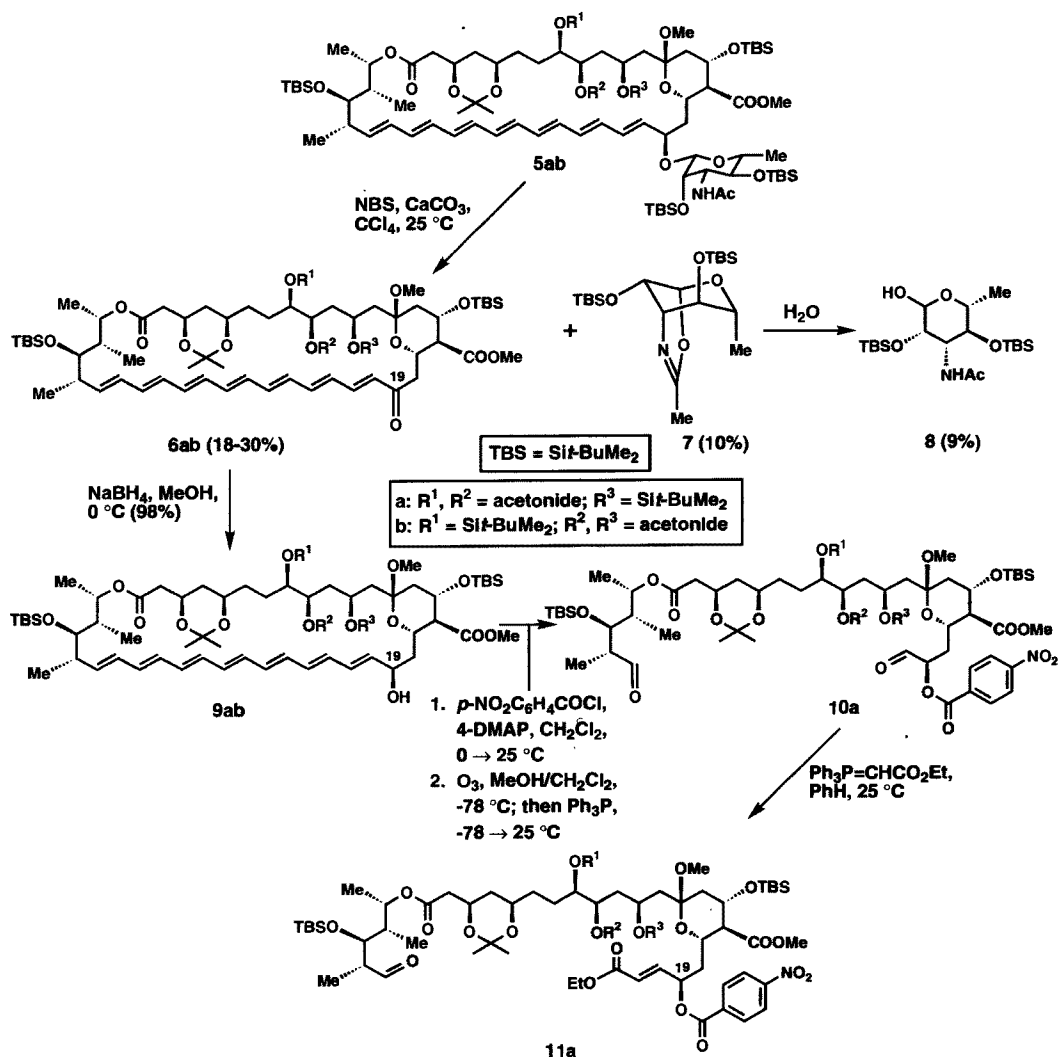
Scheme 2. Mechanistic rationale for the oxidative deglycosidation of amphotericin B (**1**).

undergo intramolecular capture by the acetamide group leading to bicyclic system **VIa** (or **VIb**), a potential precursor to mycosamine derivative **VII**. Indeed, this scenario proved to be quite viable as *N*-bromosuccinimide (NBS) in CCl_4 was shown to be an effective cleaving agent, furnishing enone **IV** and bicyclic compound **VIa** from derivative **I**. The novel heterocycle **VIa** is susceptible to facile hydrolysis to monocyclic system **VII**, although it can be isolated by careful chromatographic procedures and characterized.

A demonstration of the usefulness of this deglycosidation reaction in the preparation of amphotericin B aglycon derivatives is shown in Scheme 3. Exposure of amphotericin B derivatives **5ab** to NBS and CaCO_3 in CCl_4 results in the formation of heptaenones **6ab** in 18–30% yield (two isomers) together with bicyclic system **7** (10%) and mycosamine derivative **8** (9%).

Following the successful removal of the aglycon from the carbohydrate fragment, the reduction of the resulting heptaenone **6** was examined. Molecular models of this compound suggested two preferred yet distinct conformations (with the carbonyl group pointing β or α with respect to the plane of the paper). However, in the absence of meaningful calculations, it was not possible to define the thermodynamically most stable conformer.⁷ It was, nonetheless, expected that peripheral attack of a reducing agent on the carbonyl of **6** would deliver one stereoisomer in a highly, if not completely, stereoselective manner. In practice, this expectation was fully met. Not only is the NaBH_4 reduction of **6ab** efficient (98%), it also produces a single stereoisomer. The configuration of the newly generated hydroxyl group at C-19 was established at this stage by





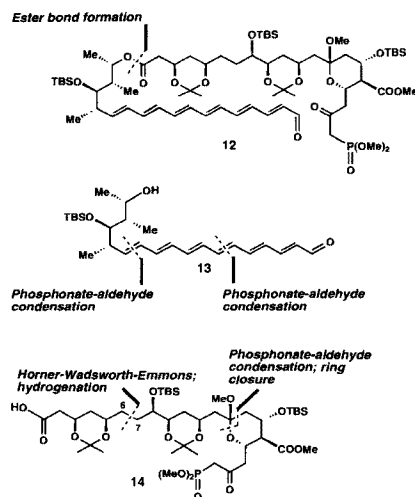
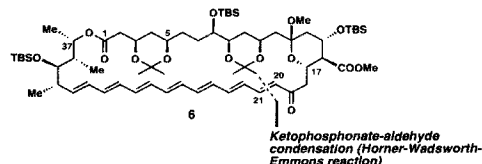
Scheme 3. Preparation of amphoteronolide B derivatives.

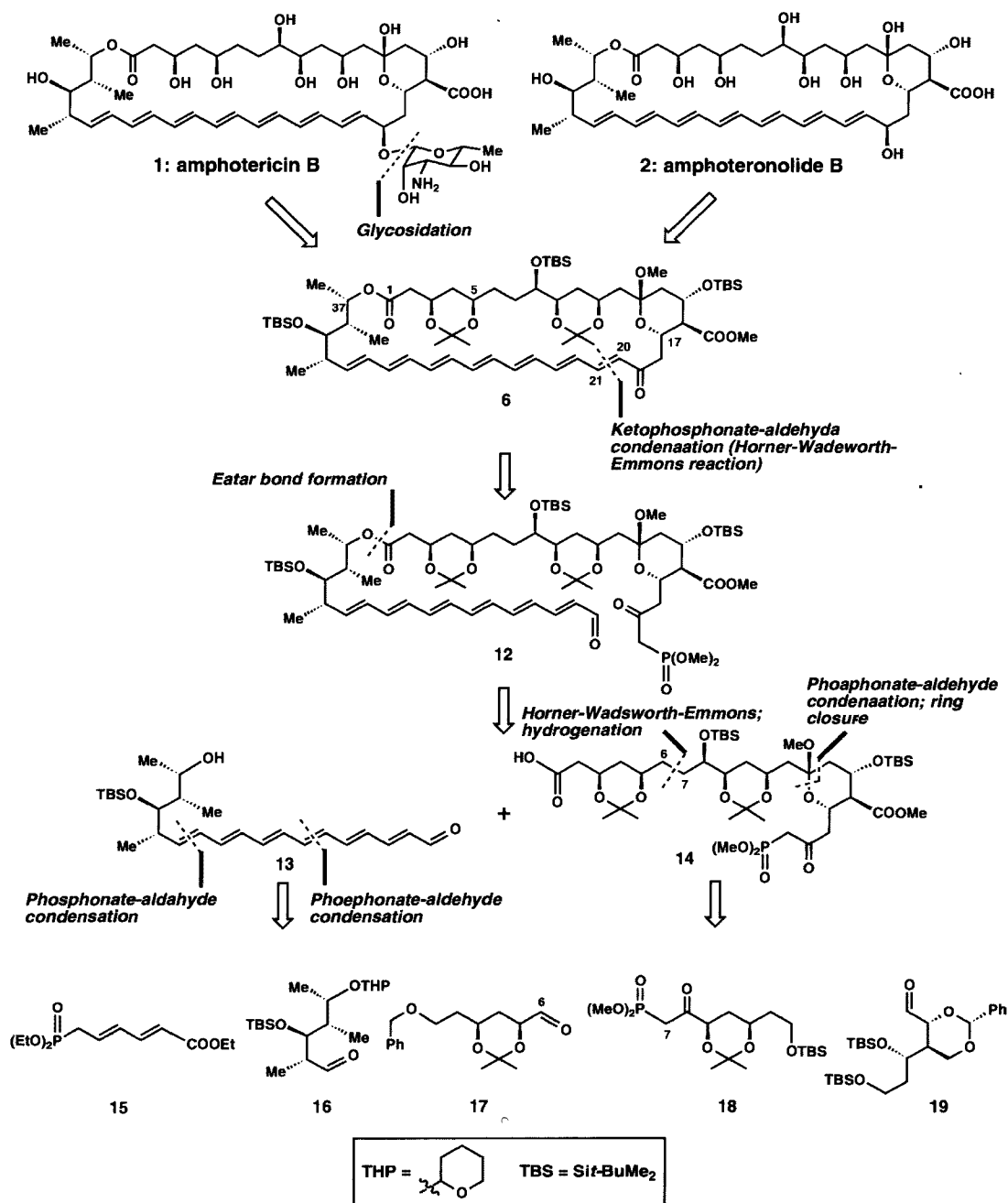
employing Nakanishi's circular dichroism (CD) method.⁸ Specifically, compound **11a** (Scheme 3), prepared from **9a** by esterification, followed sequentially by ozonolysis and Wittig condensation, exhibits a negative Cotton effect in its CD spectrum indicating a (19*R*) configuration for the series **9a–11a**. It was also established at this stage that intermediates **9ab** could serve as precursors to amphoteronolide B (**2**) via fluoride-induced desilylation, followed by acid treatment (acetonide hydrolysis) and exposure to aqueous base (methyl ester saponification). These results established a sequence for the final stages of a projected total synthesis of amphoteronolide B (**2**) and demonstrated the potential of intermediates **9ab** as precursors to amphotericin B (**1**).

The body of chemistry described above for amphotericin B (**1**) allowed, for the first time, the preparation of a series of novel derivatives of this polyene macrolide antibiotic and set the stage for a total synthesis of this target molecule. Below we unfold the adventure that led to the accomplishment of this goal.^{9,10}

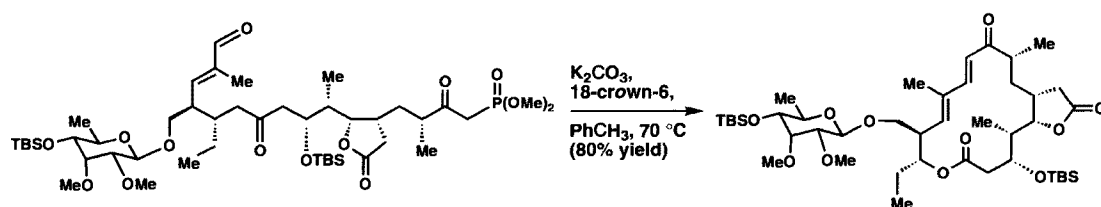
24.2 Retrosynthetic Analysis and Strategy

The general strategy for the construction of amphotericin B (**1**) and its aglycon (**2**) is based on the retrosynthetic analysis shown in Scheme 4. The strategy identifies heptaenone **6** as the central intermediate from which both **1** and **2** may be generated. Thus, it was anticipated that stereocontrolled reduction of the ketone carbonyl in **6**, or of a compound derived from **6**, would lead to an amphoteronolide B derivative from which target **2** could be obtained. On the other hand, glycosidation of amphoteronolide B derivatives derived from **6** with a suitable mycosamine equivalent, followed by functional group manipulations, was expected to provide a viable pathway towards amphotericin B (**1**). Despite the many macrolide-forming reactions available at the time of inception of these plans,¹¹ the construction of heptaenone **6**, due to its size and complexity, presented a formidable problem. Inspection of **6** reveals two obvious strategic bonds for disconnection that are suitable for macrocyclization – the lactone linkage and the C20–C21 double bond. On the basis of previous successes in the macrolide field, particularly in the series of 16-membered ring compounds exemplified by tylosin¹² (Scheme 5), a ketophosphonate–aldehyde condensation seemed suitable as the key macrocyclization step for a synthesis of **6**. Thus, ketophosphonate aldehyde **12** presented itself as a potential precursor to **6**. The rigid polyene system, the numerous substituents, and the pyran and acetonide ring systems in **12** were expected to play a positive role in the cyclization of this precursor by decreasing the degrees of rotational freedom of the open chain (seco aldehyde). Key intermediate **12** lends itself to several structurally simplifying retrosynthetic maneuvers. Disconnection of **12** at the central ester bond furnishes the two advanced intermediates **13** and **14**, uncovering a rather convergent strategy. Additional convergency can be introduced into the scheme by the remaining disconnections indicated in Scheme 4, leading to key building blocks **15–19** as starting points. It was anticipated that compounds **13** and **14** could be elaborated from these five building blocks via pathways featuring the Horner–Wadsworth–Emmons (HWE) modification of the Wittig reaction.¹³ The synthesis of **13** could conceivably be achieved through a sequence that employs two equivalents of **15** and one equivalent of **16**. In the synthetic direction, the union of intermediates **15** and **16** through a phosphonate–aldehyde condensation, followed by an ester reduction/oxidation sequence could





Scheme 4. Retrosynthetic analysis of amphotericin B (1) and amphoteronolide (2).

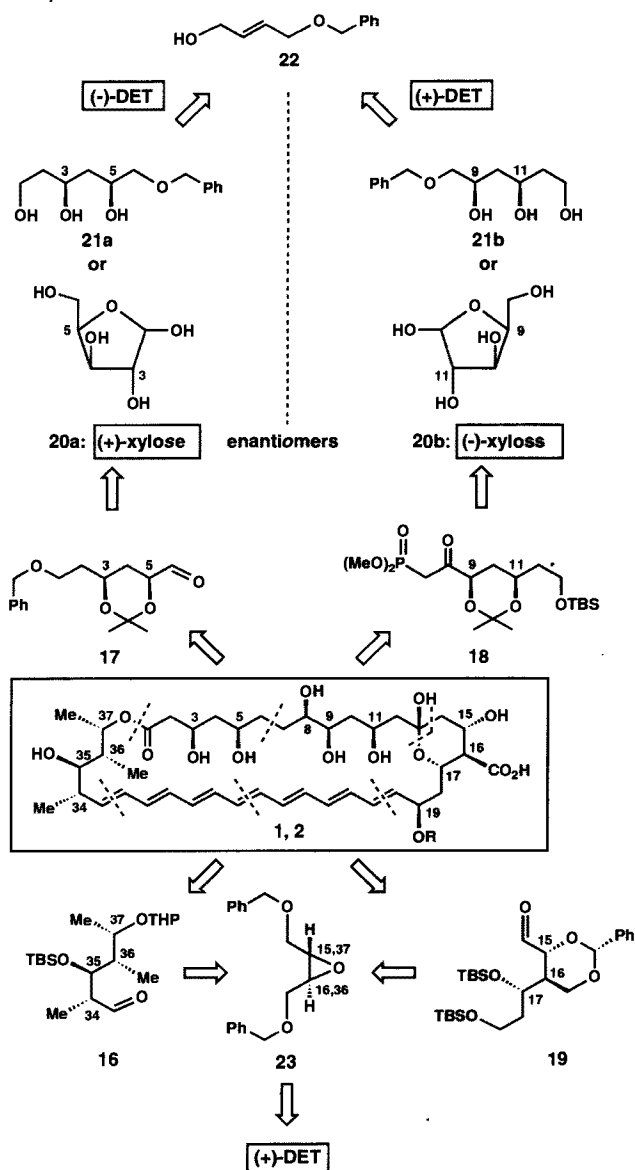


Scheme 5. Ketophosphonate–aldehyde condensation in the total synthesis of a tylosin system.

furnish a triene aldehyde. Subsequent conversion of this substance to **13** could then be achieved through a second phosphonate–aldehyde condensation with **15** followed by standard functional group manipulations.

The HWE reaction was also expected to play a pivotal role in the construction of compound **14**. It will be noted that HWE coupling of compounds **17** and **18** would furnish an α,β -unsaturated ketone (see intermediate **64**, Scheme 14). Although the *trans* $\Delta^{6,7}$ double bond contained within this substance is not present in key intermediate **14**, the adoption of a HWE bond construction to unite compounds **17** and **18** was considered desirable because the Wittig-type reaction is among the most reliable and mild carbon–carbon bond forming processes in organic synthesis. A sequence of functional group manipulations would then set the stage for another convergent HWE coupling reaction using aldehyde **19** as the electrophilic component. Appropriate modifications could then complete the synthesis of key intermediate **14**. Further retrosynthetic analysis of **14** is presented in Scheme 13 and will be discussed later in the chapter. Finally, the desire to deliver the target molecules in their naturally occurring enantiomeric forms influenced the synthetic plan.

In the selection of suitable chiral starting materials for the total synthesis of amphotericin B (**1**) and amphoteronolide B (**2**), the recognition of subtle symmetry in the targets played a crucial role. The retrosynthetic analysis presented in Scheme 6 (for **1**, **2**, and **16–19**) focuses on these symmetry elements, and leads to the design of a strategy that utilizes the readily available enantiomers of xylose and tartaric acid as starting materials and/or chiral auxiliaries to secure optically active materials.¹⁴ Thus by following the indicated disconnections in Scheme 6, the initially generated key intermediates **16–19** can be traced to epoxide **23** (**16,19** \Rightarrow **23**), (+)-xylose **20a** (**17** \Rightarrow **20a**), and (–)-xylose **20b** (**18** \Rightarrow **20b**). Alternatively, intermediates **17** and **18** can be traced to the enantiomeric tetraol derivatives **21a** and **21b**, respectively. In the synthetic direction, readily available (–)-diethyl D-tartrate [(–)-DET] and (+)-diethyl L-tartrate [(+)-DET] may be used as chiral ligands to build



Scheme 6. Symmetry recognition and retrosynthetic analysis of amphotericin B (1) and amphoteronolide B (2).

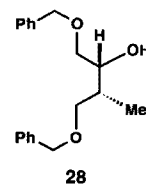
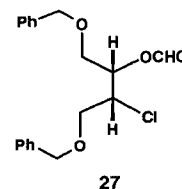
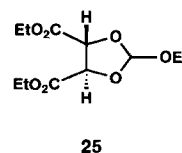
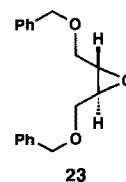
the requisite absolute stereochemistry in intermediates **21a** and **21b**, respectively, from achiral allylic alcohol **22** by means of the powerful Sharpless asymmetric epoxidation technology.¹⁵ The readily available (+)-DET could also be utilized to synthesize C_2 -symmetric epoxide **23** in enantiomerically pure form. The numbering on the structures in Scheme 6 indicates the origin of selected stereocenters in amphotericin B (**1**) and amphoteronolide B (**2**). With a general strategy in hand, the total synthesis of **1** and **2** were undertaken.

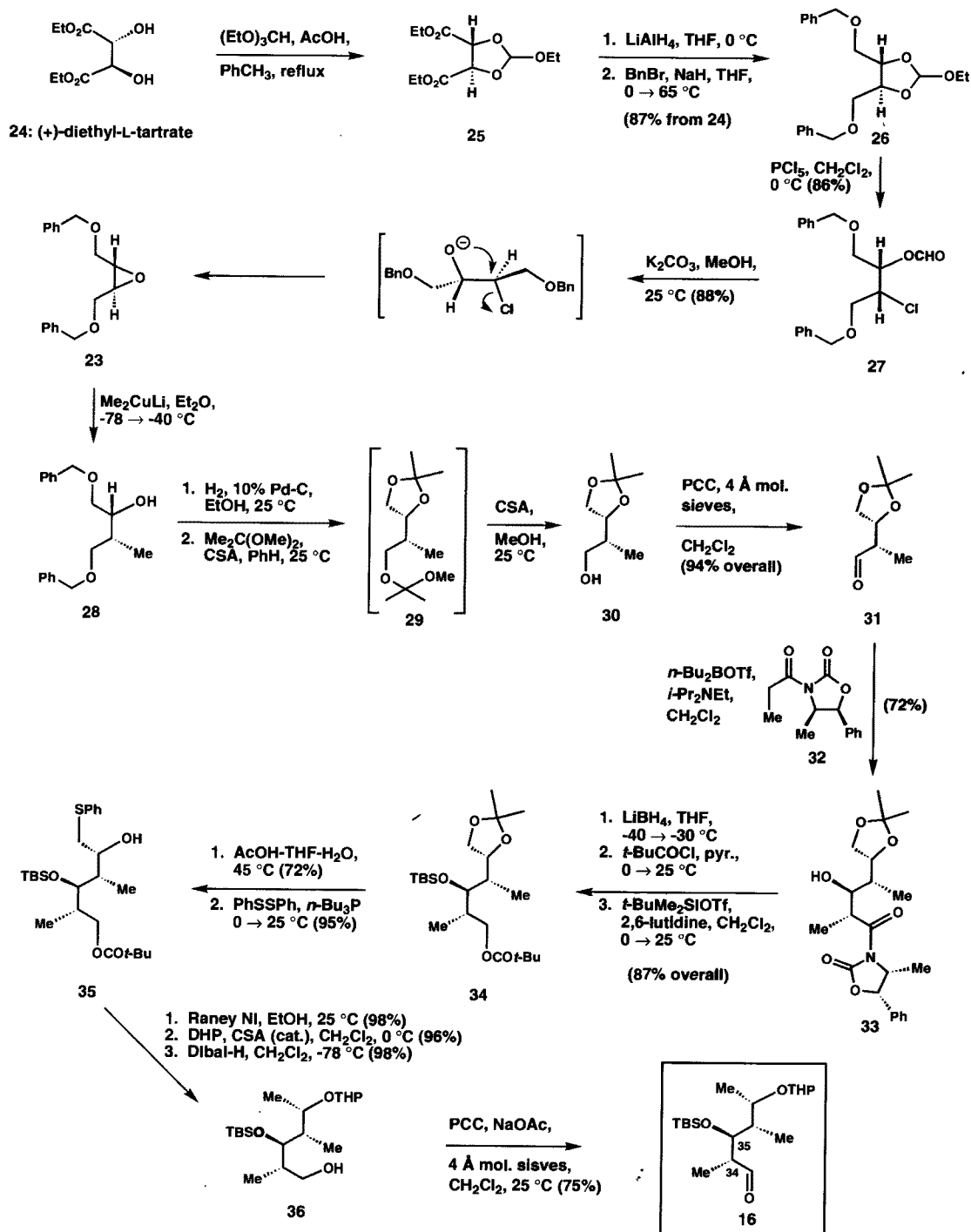
24.3 Total Synthesis

24.3.1 Construction of Building Blocks **16** and **19**

The construction of key intermediate **16** is summarized in Scheme 7. It was recognized that compound **16** could be fashioned from the versatile chiral building block **23**. Through a previously established synthetic pathway,¹⁶ epoxide **23** can be prepared in enantiomerically pure form from (+)-diethyl L-tartrate (**24**). Thus, the combined action of glacial acetic acid and triethyl orthoformate on **24** in refluxing toluene permits the simultaneous protection of the contiguous secondary hydroxyls in the form of a cyclic orthoformate (intermediate **25**). Reduction of both ester functions in **25** with lithium aluminum hydride furnishes a diol which can subsequently be converted to bis(benzyl ether) **26** in the conventional way with benzyl bromide and sodium hydride (87% overall yield from **24**). Interestingly, when cyclic orthoformate **26** is treated with phosphorous pentachloride, a ring-opening reaction, with inversion of configuration, takes place to give chloroformate **27** in 86% yield. Enantiomerically pure epoxide **23** can then be formed in 88% yield by treatment of **27** with potassium carbonate in methanol. In this reaction, the alkoxide ion formed by solvolysis of the formate function in **27** displaces the chloride in an intramolecular S_N2 reaction with inversion of configuration (see arrows).

The C_2 -symmetric epoxide **23** (Scheme 7) reacts smoothly with carbon nucleophiles. For example, treatment of **23** with lithium dimethylcuprate proceeds with inversion of configuration, resulting in the formation of alcohol **28**. An important consequence of the C_2 symmetry of **23** is that the attack of the organometallic reagent upon either one of the two epoxide carbons produces the same product. After simultaneous hydrogenolysis of the two benzyl ethers in **28**, protection of the 1,2-diol as an acetonide ring can be easily achieved by the use of 2,2-dimethoxypropane and camphor-sulfonic acid (CSA). It is necessary to briefly expose the crude product from the latter reaction to methanol and CSA so that the mixed acyclic ketal can be cleaved (see **29**→**30**). Oxidation of alcohol **30** with pyridinium chlorochromate (PCC) provides alde-



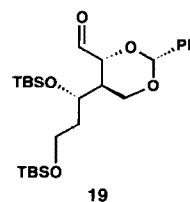
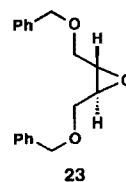


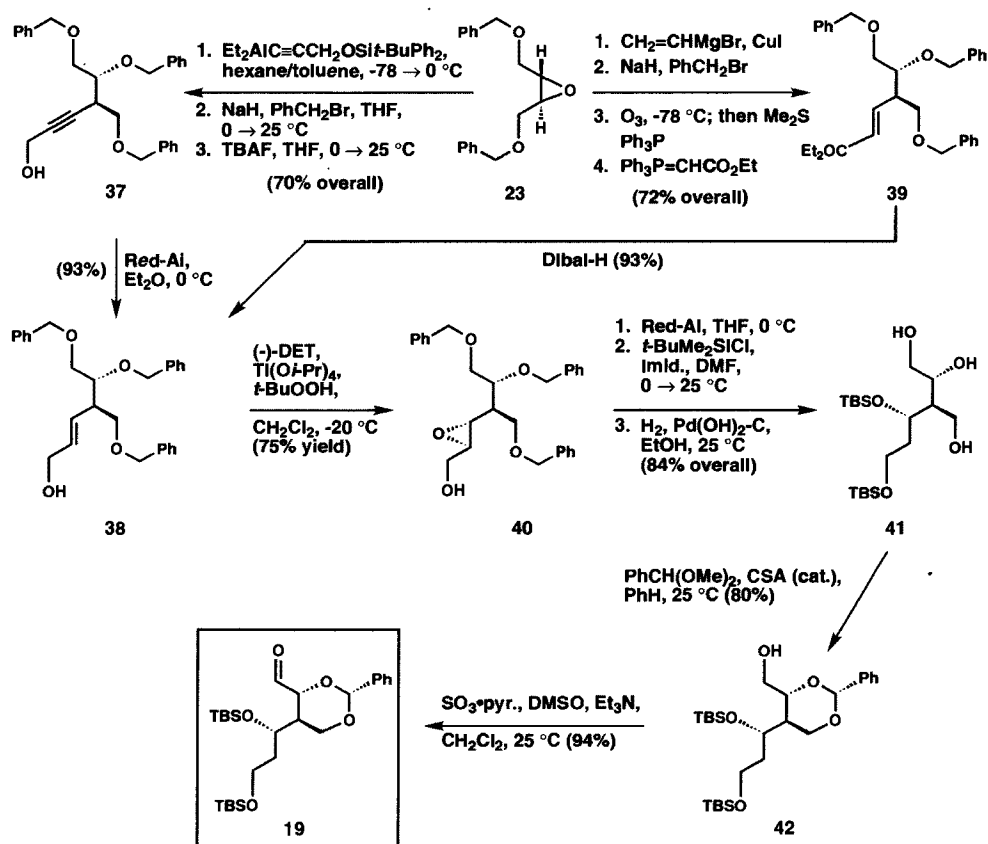
Scheme 7. Preparation of key building block 16.

hyde **31** and sets the stage for a crucial carbon–carbon bond forming reaction.

It is instructive to note that the C34–C35 bond (amphotericin numbering) in key intermediate **16** (Scheme 7) could, in principle, be conveniently constructed through an aldol condensation. The execution of an Evans asymmetric aldol reaction¹⁷ at this stage of the synthesis would be particularly productive, for it could secure the stereochemical relationships at C-34 and C-35. In the event, exposure of aldehyde **31** to the (*Z*)-boron enolate derived from oxazolidinone **32** results in the formation of an 11:1 mixture of diastereomeric aldol adducts in favor of **33** (72% yield). Compound **33** possesses the required absolute stereochemistry, and it can be easily separated from the undesired diastereomer on silica gel. Reductive removal of the chiral auxiliary in **33** with lithium borohydride (LiBH_4) provides a diol that can be converted to intermediate **34** in two straightforward steps (87% overall yield). After hydrolytic cleavage of the acetonide ring in **34**, subjection of the resulting diol to the combined action of diphenyl disulfide and tri-*n*-butylphosphine results in the formation of phenyl sulfide **35** (68% overall yield). Taking advantage of the ease with which carbon–sulfur bonds are known to be reduced, exposure of **35** to Raney nickel readily accomplishes desulfurization. Protection of the free secondary hydroxyl in the form of a tetrahydropyranyl (THP) ether, followed by reductive cleavage of the pivaloate ester using diisobutylaluminum hydride (Dibal-H), provides alcohol **36** (63% overall yield from **34**). Finally, oxidation of primary alcohol **36** with PCC furnishes key intermediate **16**.

Epoxide **23** also serves as a precursor to building block **19** as shown in Scheme 8. The key intermediate **38** can be synthesized by either of two alternative pathways. The first approach involves opening of the oxirane ring in **23** with $\text{Et}_2\text{AlC}\equiv\text{CCH}_2\text{OSi-}t\text{-BuPh}_2$ to afford, after standard protecting group chemistry, derivative **37**. Stereoselective reduction of **37** with sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al) then gives the *trans* allylic alcohol **38** in high overall yield. The second approach to intermediate **38** commences with opening of the oxirane ring in **23** with vinylmagnesium bromide/cuprous iodide to afford, after conventional manipulations, *trans* α,β -unsaturated ester **39** as the major geometrical isomer (72% overall yield). Intermediate **38** is then formed upon reduction of **39** with Dibal-H (93% yield). Sharpless asymmetric epoxidation¹⁵ of **38** [(–)-DET] furnishes epoxide **40**, which is subsequently converted to derivative **41** by standard methods as outlined in Scheme 8. Selective formation of the six-membered benzylidene¹⁸ acetal to give **42** is easily achieved with $\text{PhCH}(\text{OMe})_2$ and CSA in benzene solution (80% yield). Finally, compound **42** can be smoothly oxidized with $\text{SO}_3\cdot\text{pyr.}$ complex to provide key intermediate **19** (94% yield).

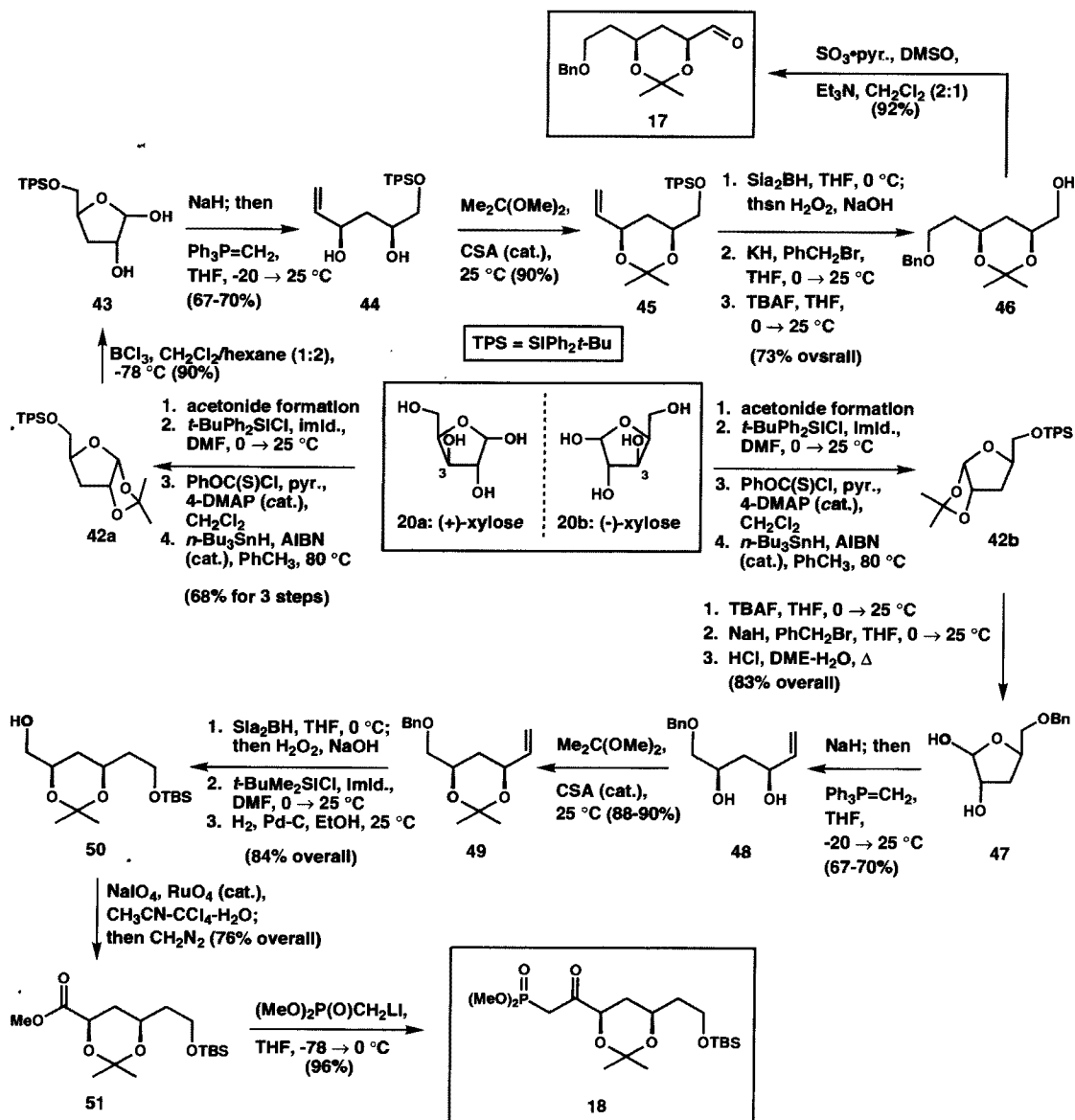




Scheme 8. Preparation of key building block **19**.

24.3.2 Construction of Building Blocks **17** and **18**: The Carbohydrate Approach

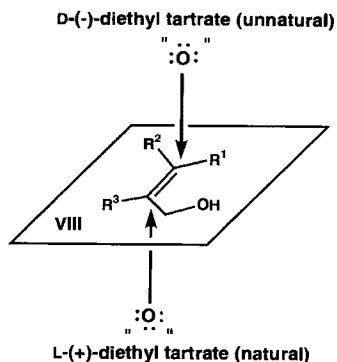
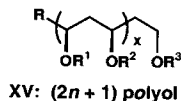
With (+)- and (–)-xylose (**20a** and **20b**, respectively) as enantiomerically pure starting materials, building blocks **17** and **18** can be constructed (see Scheme 9). This requires proper functionalization of the carbohydrate framework and deoxygenation at C-3. Thus, **20a** is converted to monoacetone derivative **42a** by standard protections, followed by deoxygenation as indicated in Scheme 9. Alternatively, the requisite reduction of C-3 can be achieved via reduction of a C3–iodine bond with superhydride (LiEt_3BH). Lactol **43**, liberated from **42a** by the action of BCl_3 , can be converted to **45**, via **44**, by standard olefination and acetonide formation procedures. Finally, functional group manipulation leads sequentially to **46** and **17** in high overall yield as outlined in Scheme 9. The construction of key intermediate **18** from (–)-xylose (**20b**) proceeds



initially along similar lines as described above for **17** through intermediate **42b**. Exchange of the silyl protecting group for a benzyl ether, followed by cleavage of the isopropylidene ketal leads to intermediate **47**, which is carried through to the subtarget **18** in straightforward fashion via intermediates **48–51** as described in Scheme 9.

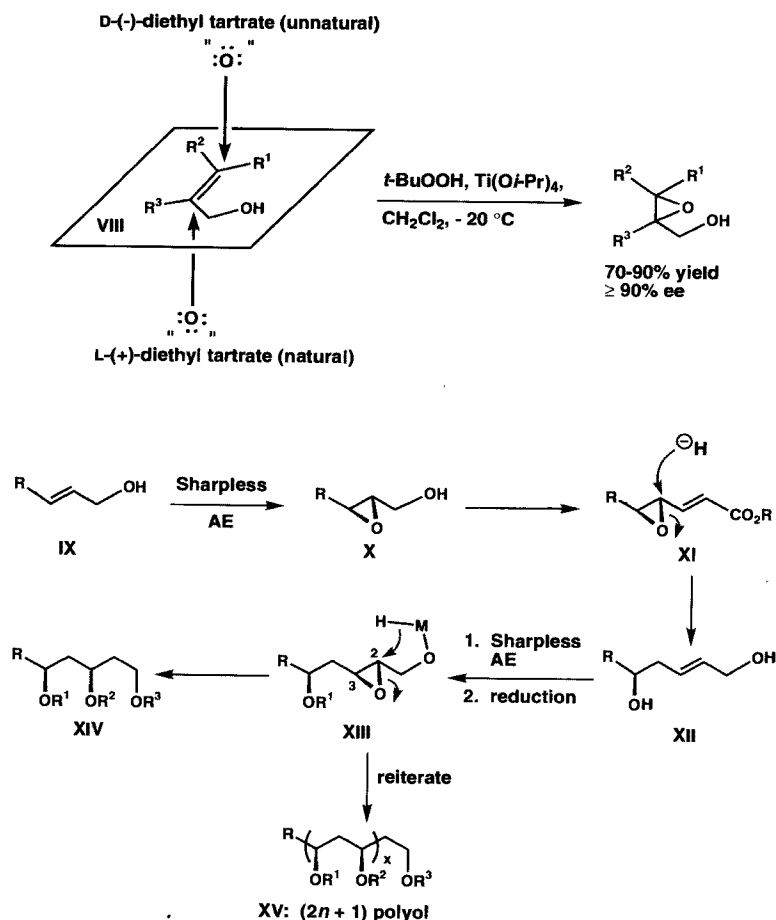
24.3.3 Construction of Building Blocks **17** and **18**:

The Sharpless Asymmetric Epoxidation Approach



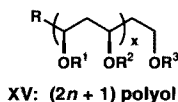
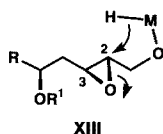
A glance at the structures of several macrolide antibiotics of the polyene class, including amphotericin B (**1**), reveals the presence of fragments belonging to the series 1,3,5 ... $(2n+1)$ polyols. Aiming for a general and flexible solution to the problem of constructing such compounds, we set out to develop a procedure based upon the powerful asymmetric epoxidation reaction developed by Sharpless.¹⁵ Reported in 1980 by Katsuki and Sharpless,^{15a} the Sharpless asymmetric epoxidation (SAE) reaction (see Scheme 10 and also Chapter 19) accomplishes the stereoselective epoxidation of a wide variety of allylic alcohols, and ranks among the most valuable reactions in organic synthesis. The SAE reaction subjects an allylic alcohol to the combined action of titanium tetrakisopropoxide, *tert*-butyl hydroperoxide, and (+)- or (-)-DET and provides direct access to synthetically versatile epoxy alcohols of high stereoisomeric purity. An important attribute of the SAE reaction is that the stereochemical outcome is very predictable. For example, when a generic achiral allylic alcohol (e.g. **VIII**) (see Scheme 10) is depicted in the manner illustrated (i.e. OH group in the lower right-hand corner), the oxygen atom is delivered to the top face of the alkene when unnatural D-(-)-DET is used as the chiral ligand. On the other hand, when L-(+)-DET is employed as the chiral ligand, an oxygen atom is delivered to the bottom face of the alkene. In either case, the SAE reaction exhibits exceptional enantiofacial selectivity (often *ca.* 100:1), and tolerates a wide variety of functional groups. For example, if an allylic alcohol possesses more than one double bond, only that of the allylic alcohol is oxidized.

Interestingly, even when a chirality center (or centers) is in the vicinity of the allylic alcohol, delivery of the oxygen atom to either alkene diastereoface is possible with good selectivity simply by choosing the appropriate tartrate ligand; even in the crucial “mismatched” case,¹⁹ the titanium–tartrate complex is often capable of overwhelming the inherent diastereofacial preference of the substrate molecule. The procedure originally reported by Katsuki and Sharpless^{15a} has been modified. These modifications and the synthetic utility of the SAE reaction have been addressed in several excellent reviews^{15b–g} and will not be discussed here. It is important to note that the SAE reaction can be successfully conducted with a catalytic amount of the titanium–tartrate complex provided that molecular sieves are added to the reaction medium.



Scheme 10. General approach to (2n + 1) polyol systems.

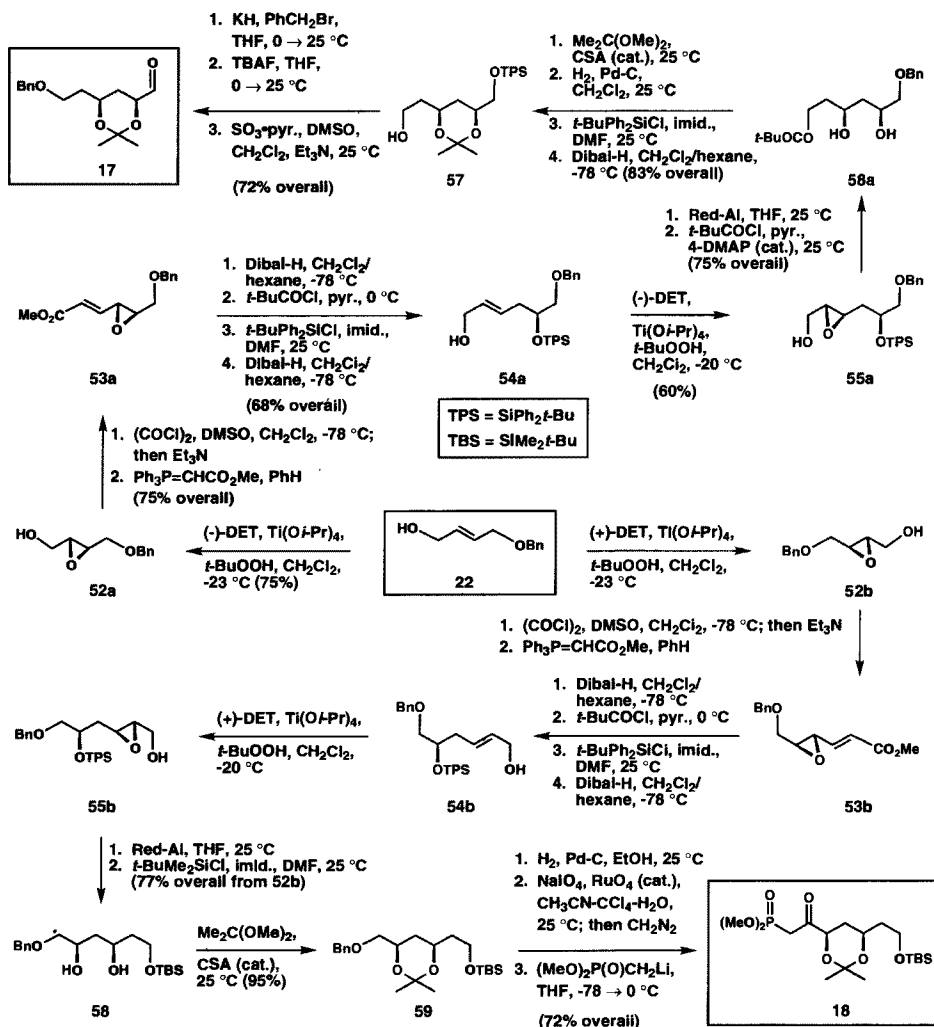
The incorporation of the powerful SAE reaction into an iterative strategy for the synthesis of 1,3,5 ... (2n+1) polyols is outlined in Scheme 10. The designed sequence employs readily available *trans* allylic alcohols of the type **IX**, and utilizes reliable reaction sequences. Thus, subjection of **IX** to SAE would afford **X** (or, if R is achiral, its enantiomer, if so desired). Oxidation of epoxy alcohol **X** to the corresponding aldehyde, followed by a stereoselective two-carbon Wittig homologation, could then give unsaturated ester **XI**. The basic plan relies on the premise that the C–O bond adjacent to the olefinic site would suffer preferential cleavage under reductive conditions. It was thus anticipated that regioselective reductive opening of the oxirane ring in **XI**, with concomitant reduction of the ester function, would result in the formation of diol **XII**. After protection of the secondary hydroxyl group, execution of a second SAE using (+)-DET as the chiral ligand could afford β -epoxy alco-



hol **XIII**. An important reason why epoxy alcohols are so useful as synthetic intermediates is that they are amenable to a variety of selective transformations.²⁰ For example, it is known that the action of Red-Al on a 2,3-epoxy alcohol such as **XIII** (-M) can accomplish a regioselective (OH-directed) reductive cleavage of the C2–O bond to give a 1,3-diol (see **XIV**; R², R³ = H).^{21,22} It is proposed that the free hydroxyl group of the epoxy alcohol reacts with Red-Al [NaAlH₂(OCH₂CH₂OMe)₂] to give an aluminate, and that an internal delivery of hydride permits a regioselective oxirane ring cleavage. Reiteration of the reaction sequence described above could provide access to higher homologues (**XV**) as desired. This SAE-based strategy for the synthesis of 1,3,5 ... (2n+1) polyols is concise and very flexible. It is important to note that absolute and relative stereochemistry can be secured simply by employing the appropriate tartrate ligand in the SAE reaction.

Scheme 11 summarizes the syntheses of key intermediates **17** and **18** according to this general strategy. Thus, *trans* allylic alcohol **22** serves as the common starting material for the synthesis of both **17** and **18**. Sharpless asymmetric epoxidation of **22** with (–)-DET furnishes epoxy alcohol **52a** (75 % yield), which can subsequently be converted to epoxy ester **53a** via sequential Swern oxidation and Wittig reaction (75 % overall). Treatment of **53a** with Dibal-H accomplishes the desired cleavage of the oxirane ring and the reduction of the methyl ester, giving a 1,5-diol. Selective protection of the less hindered primary hydroxyl in the form of a pivaloate ester, followed sequentially by silylation of the secondary hydroxyl and reductive cleavage of the pivaloate ester, provides allylic alcohol **54a** (68 % from **53a**). The latter substance is poised for an SAE reaction. Indeed, asymmetric epoxidation of **54a** with (–)-DET affords epoxy alcohol **55a** (60 % yield). Hydroxyl-directed cleavage of the oxirane ring in **55a** with Red-Al, followed by acylation of the less hindered primary hydroxyl with pivaloyl chloride results in the formation of diol pivaloate **56a** (75 % overall). Incidentally, during the course of the Red-Al reduction of **55a**, the *tert*-butyldiphenylsilyl ether is cleaved. Simultaneous protection of the secondary hydroxyl groups in **56a** in the form of an isopropylidene ketal is easily achieved in the conventional way with 2,2-dimethoxypropane and a catalytic amount of CSA. A trivial protecting group exchange sequence, followed by reductive cleavage of the pivaloate ester with Dibal-H then provides alcohol **57** (63 % yield from **56a**). Finally, protection of the primary hydroxyl group as a benzyl ether, followed sequentially by fluoride-induced cleavage of the silyl ether and oxidation, completes the synthesis of aldehyde **17** (72 % overall yield).

The construction of key intermediate **18** can be conducted along similar lines. Sharpless asymmetric epoxidation of allylic alcohol **22** using (+)-DET furnishes epoxy alcohol **52b** (Scheme 11). Subjection of the latter substance to the same six-step reaction sequence as that leading to **54a** provides allylic alcohol **54b** and sets the stage for a second SAE reaction. With (+)-DET as the

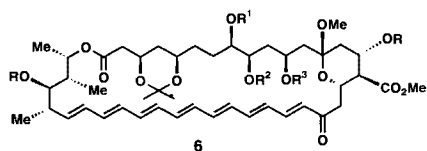


Scheme 11. Preparation of key building blocks **17** and **18**: The SAE approach.

chiral ligand, asymmetric epoxidation of **54b** affords epoxy alcohol **55b**, a substance that can easily be converted to diol **58** upon sequential treatment with Red-Al and *tert*-butyldimethylsilyl chloride. Simultaneous protection of the free secondary hydroxyl groups in **58** in the form of an isopropylidene ketal gives intermediate **59** (95% yield). Hydrogenolysis of the benzyl ether in **59**, followed by stepwise oxidation and esterification, then provides a methyl ester, which reacts smoothly with $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{Li}$ to give key intermediate **18** (72% yield from **59**).

The described chemistry leading to the synthesis of key building blocks **16–19** sets the stage for the completion of the total synthesis of both amphotericin B (**1**) and its aglycon, amphoteronolide B (**2**).

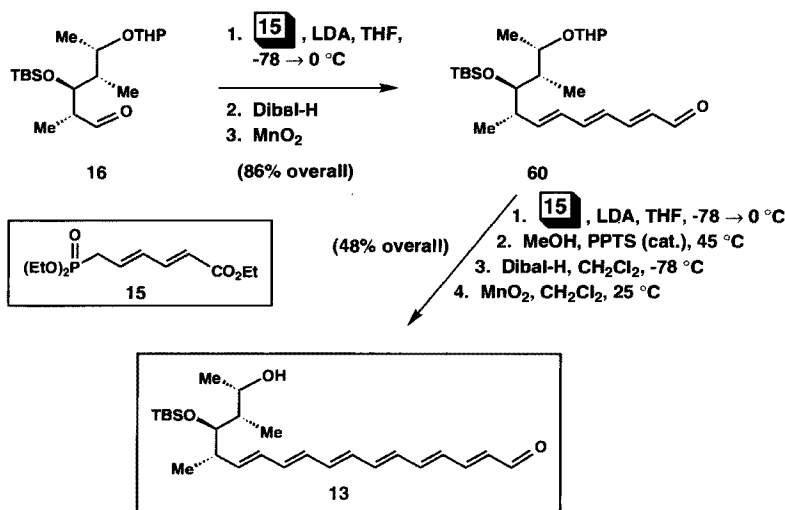
24.3.4 Completion of the Synthesis of Amphoteronolide B



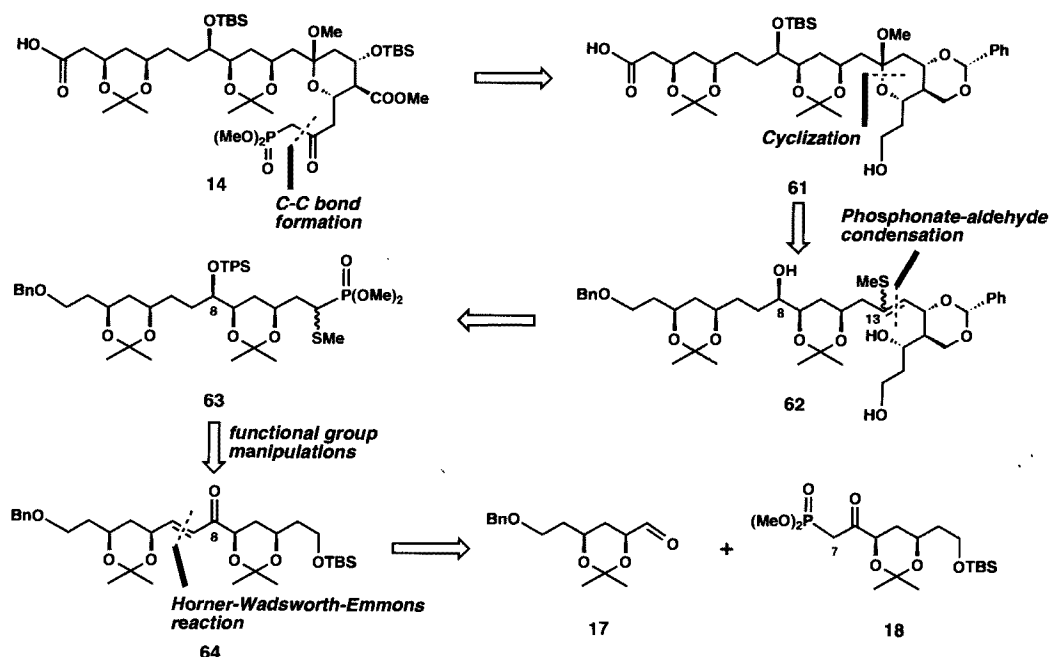
With the key building blocks **16**–**19** secured, attention can now be turned to their coupling and elaboration to the cyclic heptaenone **6** (Scheme 4), from which both amphoteronolide B (**2**) and amphotericin B (**1**) could be generated. To this end, the advanced intermediates, hydroxy aldehyde **13** and ketophosphonate carboxylic acid **14** (Scheme 4), were synthesized as outlined below.

The strategy for the construction of **13** from aldehyde **16** with two units of phosphonate **15** is summarized in Scheme 12. As expected, aldehyde **16** condenses smoothly with the anion derived from **15** to give, as the major product, the corresponding *E,E,E*-triene ester. Reduction of the latter substance to the corresponding primary alcohol with Dibal-H, followed by oxidation with MnO₂, then furnishes aldehyde **60** in 86 % overall yield. Reiteration of this tactic and a simple deprotection step completes the synthesis of the desired intermediate **13** in good overall yield and with excellent stereoselectivity.

The synthetic strategy for the construction of ketophosphonate carboxylic acid **14** was designed on the basis of the retrosynthetic analysis presented in Scheme 13. Subtarget **14** could, in principle, be derived from **61** by appropriate functional group interchange and introduction of a C₁ unit carrying the phosphonate functionality. With the focus on the phosphonate–aldehyde condensation as the potential coupling reaction, the following steps were devised. The tetrahydropyran system in **61** can be dismantled by rupture of the indicated bond, providing vinyl sulfide **62**. The design of this key intermediate allows the possibility of regioselective ring closure to **61**, and provides a convenient site for molecular sim-



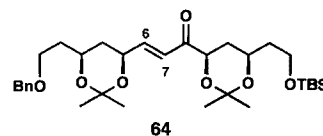
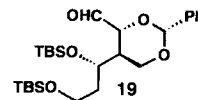
Scheme 12. Synthesis of advanced intermediate **13**.

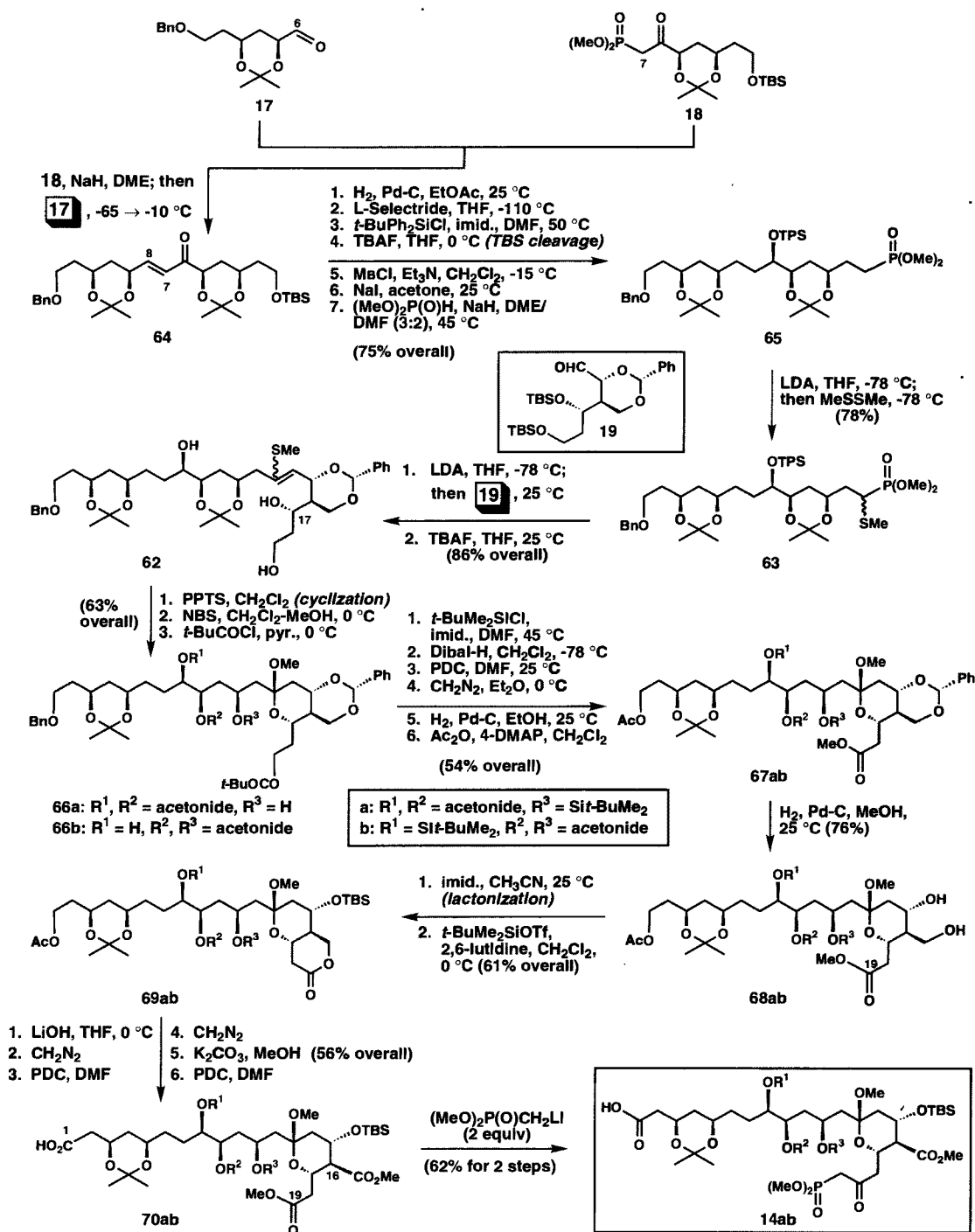


Scheme 13. Retrosynthetic analysis of ketophosphonate carboxylic acid **14**.

plification. Retrosynthetic cleavage of the trisubstituted double bond in **62** reveals phosphonate **63** (Scheme 13) and aldehyde **19** (Scheme 8) as potential precursors. It was then reasoned that the β -disposed C-8 hydroxyl group could be generated by stereoselective reduction of a C-8 ketone, and that introduction of a double bond in conjugation with this carbonyl would permit the reliable HWE reaction (ketophosphonate-aldehyde condensation) to be used in the coupling process. Thus, intermediate **63** can be traced to enone **64**. Finally, dissection of enone **64**, in the manner illustrated in Scheme 13, furnishes intermediates **17** and **18** as starting points for the synthesis.

The synthesis of ketophosphonate carboxylic acid **14** commences with the convergent union of intermediates **17** and **18** (see Scheme 14). You will note that the electron-withdrawing phosphonate and keto functions in **18** confer considerable lability to the C7–H bonds. It is, therefore, not surprising that the action of sodium hydride on **18** easily brings about the deprotonation of **18** to give a resonance-stabilized C-7 carbanion, the conjugate base of **18**. Now, when this stabilized anion is treated with aldehyde **17**, an intermolecular HWE reaction takes place smoothly, giving α,β -unsaturated ketone **64** in 94% yield. Although the newly introduced site of unsaturation is deleted during the course of the conversion of **64** to **14**, the HWE coupling reaction provides a most effective and mild solution to the task of constructing the key C6–C7 bond. Saturation



Scheme 14. Synthesis of advanced key intermediate **14ab**.

of the $\Delta^{6,7}$ carbon-carbon double bond in **64**, followed by diastereoselective reduction of the C-8 ketone carbonyl with lithium tri-*sec*-butylborohydride (L-Selectride) produces the desired C-8 β -alcohol. After protection of this alcohol as a *tert*-butyldiphenylsilyl ether, the execution of a conventional sequence of functional group manipulations permits the assembly of phosphonate **65** (75 % yield from **64**). The action of lithium diisopropylamide (LDA) on **65** results in the formation of a phosphonate-stabilized carbanion, which can subsequently be quenched with dimethyl disulfide to give **63** as an equimolar mixture of epimeric sulfides (78 % yield). Deprotonation of **63** with LDA, followed by condensation of the resulting α -lithiophosphonate with aldehyde **19** furnishes, after fluoride-induced cleavage of the three silyl ethers, vinyl sulfide **62** (86 % overall yield).

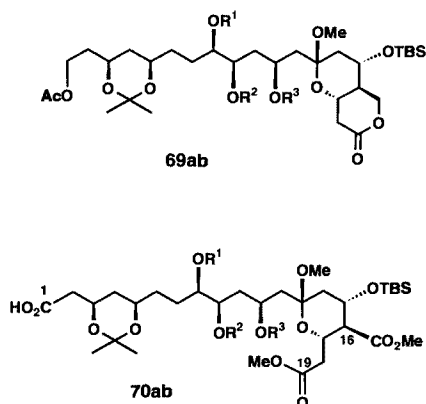
A crucial stage in the synthesis of key intermediate **14** has been reached. It was hoped that the vinyl sulfide function in **62** (Scheme 14) would permit a regioselective cyclization to give the requisite pyran ring. Gratifyingly, treatment of **62** with pyridinium *para*-toluenesulfonate (PPTS) accomplishes the desired cyclization to give a monothioacetal. It is presumed that the action of PPTS on **62** results in the formation of a transitory thionium ion intermediate which is captured by the proximal C-17 hydroxyl group. Oxidative solvolysis of the monothioacetal with *N*-bromosuccinimide (NBS) in CH_2Cl_2 -MeOH, followed by selective acylation of the primary hydroxyl with pivaloyl chloride, provides a mixture of isomeric acetonides **66a** and **66b** (ratio variable). Evidently, acid-induced acetonide migration occurs under the conditions of the ring closure reaction. The subsequent stages of the synthesis were developed on the mixture of isomeric acetonides **66a** and **66b** because the two components were not easily separated.

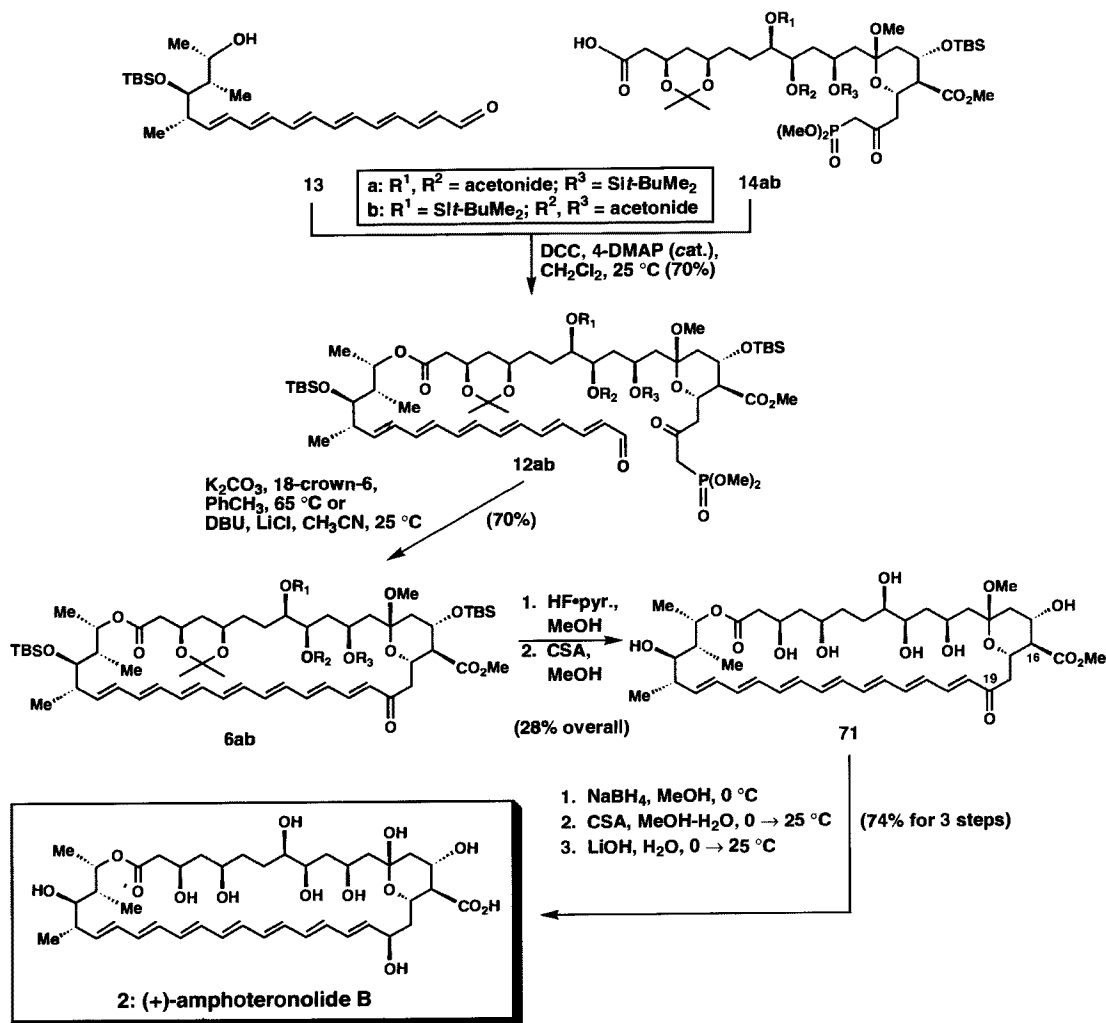
You will note that **66ab** and key intermediate **14** possess very similar structures. Intermediates **66ab** harbor the nine requisite stereocenters and can be converted to **14** through a series of conventional functional group manipulations. Exposure of **67ab**, the product of a straightforward six-step reaction sequence starting from **66ab**, to hydrogen and Pd-C for an extended period of time accomplishes the hydrogenolysis of the benzylidene acetal, providing diol **68ab** in 76 % yield. The differentiation of the two free hydroxyl groups in **68ab** is a prerequisite for the synthesis of compound **14**. A cursory examination of the structure of **68ab** reveals that the primary hydroxyl and methoxycarbonyl functions are in proximity. A useful consequence of this spatial relationship is that it ought to be possible to temporarily protect the free primary hydroxyl group in the form of a δ -lactone ring. The free secondary hydroxyl could then be protected as desired, after which the primary hydroxyl could be unveiled upon saponification of the lactone ring. Reduction of this plan to practice was achieved without incident. Thus, treatment of **68ab** with imidazole in acetonitrile induces the desired lactonization. Intermediates **69ab** can then be formed upon silylation of the remaining secondary hydrox-

yl group with *tert*-butyldimethylsilyl triflate (61 % yield from **68ab**).

Although acetate esters can be susceptible to cleavage in the presence of aqueous base, it is possible to bring about a smooth and selective hydrolysis of the δ -lactone function in **69ab** with aqueous lithium hydroxide in THF. This hydrolytic lactone-opening reaction furnishes a free hydroxyl group at one end of the point of cleavage and a carboxyl group at the other. Esterification of the latter function with diazomethane (CH_2N_2) produces a hydroxy methyl ester, which can be converted to a bis(methyl ester) through sequential oxidation (PDC, DMF) and esterification (CH_2N_2) reactions. The terminal acetate ester can then be cleaved with basic methanol, and the resulting primary alcohol can be oxidized with PDC in DMF to give carboxylic acids **70ab** (56 % yield from **69ab**). Finally, treatment of **70ab** with three equivalents of $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{Li}$ results in the formation of key intermediates **14ab** (62 % yield). In this reaction, one equivalent of the α -lithiophosphonate reagent is consumed in an acid-base reaction with the terminal C-1 carboxyl group. This seemingly unproductive reaction is actually very important, for it furnishes a C-1 carboxylate anion, the carbonyl group of which is protected from nucleophilic addition. Although the remaining α -lithiophosphonate reagent could, in principle, react indiscriminately with the two electrophilic methoxycarbonyl groups, it was most gratifying to find that the C-19 ester carbonyl is attacked selectively. The reluctance of the C-16 methoxycarbonyl group to react under these conditions is attributed to its hindered nature.

The retrosynthetic analysis summarized in Scheme 4 identifies heptaenone **6** as a crucial intermediate from which amphotericin B (**1**) and amphoteronolide B (**2**) could be generated. Although the macrocyclic structure of **6** could conceivably be assembled through lactonization of a suitably constituted seco acid,¹¹ the option afforded by an intramolecular ketophosphonate-aldehyde condensation appeared particularly attractive in view of prior experiences in the group.¹² A task implicit in this strategy is the convergent union of key intermediates **13** and **14** through an ester linkage. As shown in Scheme 15, the coupling of compounds **13** and **14ab** can be achieved with the dehydrating agent dicyclohexylcarbodiimide (DCC) (70 % yield). It was anticipated that the conformational rigidity conferred on **12ab** by the pyran ring, the two acetonide rings, and the polyunsaturated sector would facilitate the macrocyclization step. Indeed, the crucial intramolecular ketophosphonate-aldehyde condensation can be performed successfully under mildly basic conditions [$(\text{K}_2\text{CO}_3, 18\text{-crown-6, toluene, } 65^\circ\text{C})$ ¹² or $(\text{DBU-LiCl, CH}_3\text{CN, } 25^\circ\text{C})$ ²³], furnishing heptaenone **6ab** in 70 % yield. From this point on, the total synthesis of amphotericin B (**1**) and of amphoteronolide B (**2**) diverge. The total synthesis of the aglycon can be achieved in a few straightforward steps from the major acetonide isomer **6a** (see Scheme 15). Thus, fluoride-induced cleavage of the three *tert*-butyldimethylsilyl ethers in compound **6a**, fol-





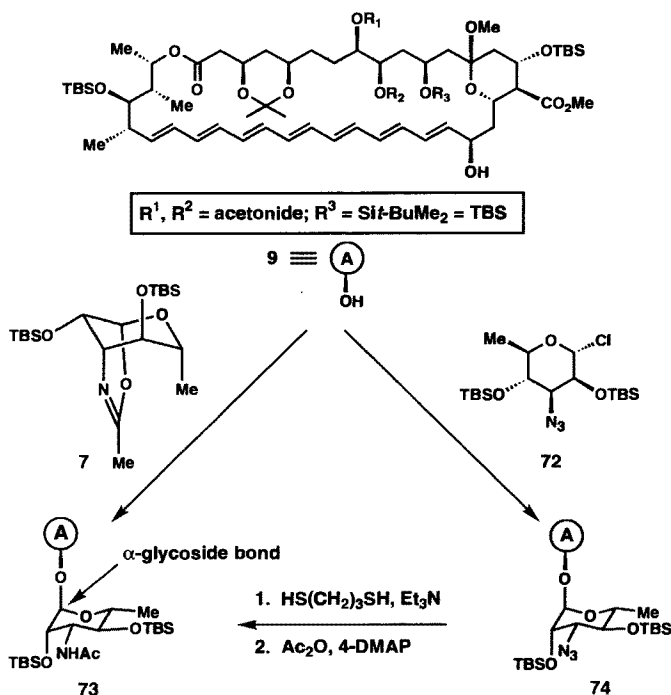
Scheme 15. Completion of the synthesis of (+)-amphoteronolide B (**2**).

lowed by acid-catalyzed solvolysis of the acetonide protecting groups, provides intermediate **71**. As was expected, based on the early degradation studies, reduction of the C-19 ketone in **71** with sodium borohydride proceeds both chemo- and stereoselectively (see Scheme 3). Finally, hydrolysis of the mixed-ketal function with CSA in aqueous methanol, followed by saponification of the methyl ester attached to C-16, provides (+)-amphoteronolide B (**2**).

24.3.5 Completion of the Synthesis of Amphotericin B

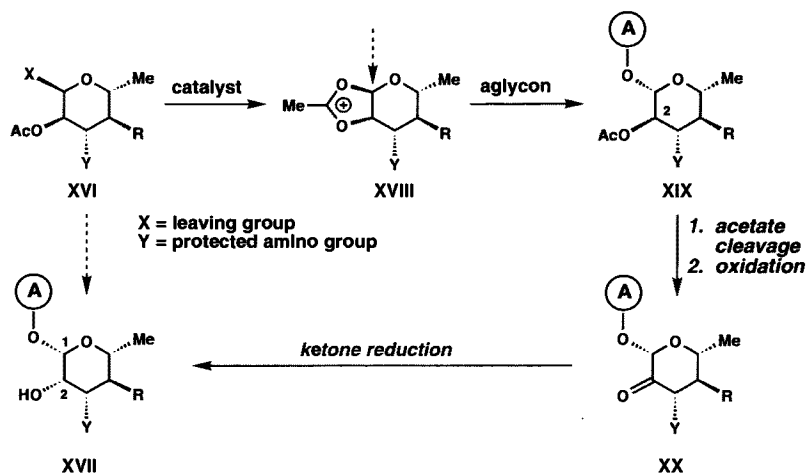
The final stages of the synthesis of amphotericin B require attachment of an appropriate mycosamine unit to a suitably protected derivative of the aglycon **2**. The glycosidation process was recognized from the outset as a formidable problem, primarily due to the following three concerns: (a) the rather unstable character of amphotericin B (**1**) and its derivatives; (b) the presence of the basic nitrogen in the carbohydrate unit; and (c) the requirement for a β -glycoside bond in a 1,2-*cis* relationship with the C-2 hydroxyl group of the carbohydrate fragment. It should be noted that the last requirement is still a particularly difficult one to fulfill in the area of oligosaccharide synthesis.²⁴ These requirements presented a significant challenge that was addressed with systematic glycosidation studies.

A number of mycosamine equivalents were synthesized and utilized in glycosidation attempts with the amphoteronolide B derivative **9** (Scheme 16). Of those examined, most failed. However, the mycosamine derivatives **7** and **72** proved interesting in that both reacted with **9** under suitable conditions to give the coupled products in reasonable yields, but unfortunately with the undesired α -linkage (Scheme 16). A conceptually new approach that ultimately led to a successful solution to the problem was therefore developed.



Scheme 16. Early glycosidation attempts.

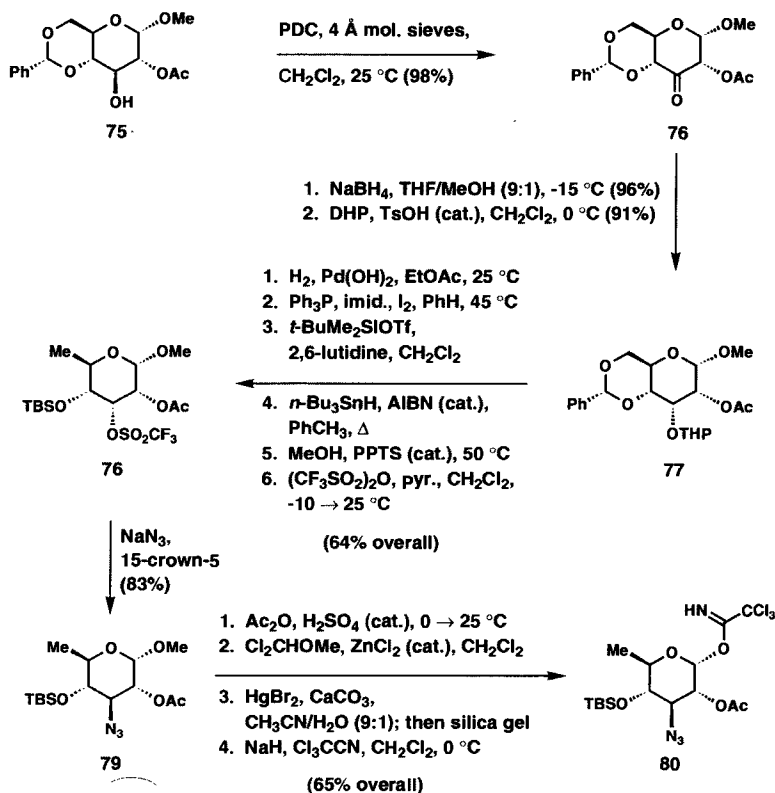
According to the new, rational approach to the glycosidation problem, a glycosyl donor equipped with an appropriately positioned C-2 stereocontrolling group (e.g. acetoxy) would be employed so that the requisite β -configuration at the anomeric position could be secured through neighboring group participation. Although this glycosyl donor would necessarily possess the unnatural configuration at C-2, it was hoped that stereochemical inversion at C-2 could be achieved after the key glycosidation step. Scheme 17 outlines the general features of this strategy. It was anticipated that exposure of a suitably activated glycosyl donor of the general type **XVI** to a Lewis acid would induce the formation of transitory acetoxonium ion **XVIII**. This reactive intermediate could then glycosylate an aglycon equivalent in a stereoselective fashion. Indeed, on the basis of abundant precedent,^{24,25} it was assumed that the attack of an aglycon equivalent upon acetoxonium ion **XVIII** would occur with inversion of configuration at the anomeric carbon, thereby securing the formation of the desired β -glycoside **XIX**. It is, nonetheless, important to stress that even if the requisite β -glycosidic bond can be constructed in this manner, the overall strategy would be successful only in the event that the errant configuration at C-2 of **XIX** could be inverted. A potentially viable solution to this problem is presented in Scheme 17. Thus, cleavage of the C-2 acetate ester in **XIX**, followed by oxidation of the resulting alcohol would be expected to furnish ketone **XX**. A stereocontrolled reduction of the ketone in **XX** could then establish the requisite 1,2-*cis* stereorelationship in **XVII**. Subsequent functional group manipulations were



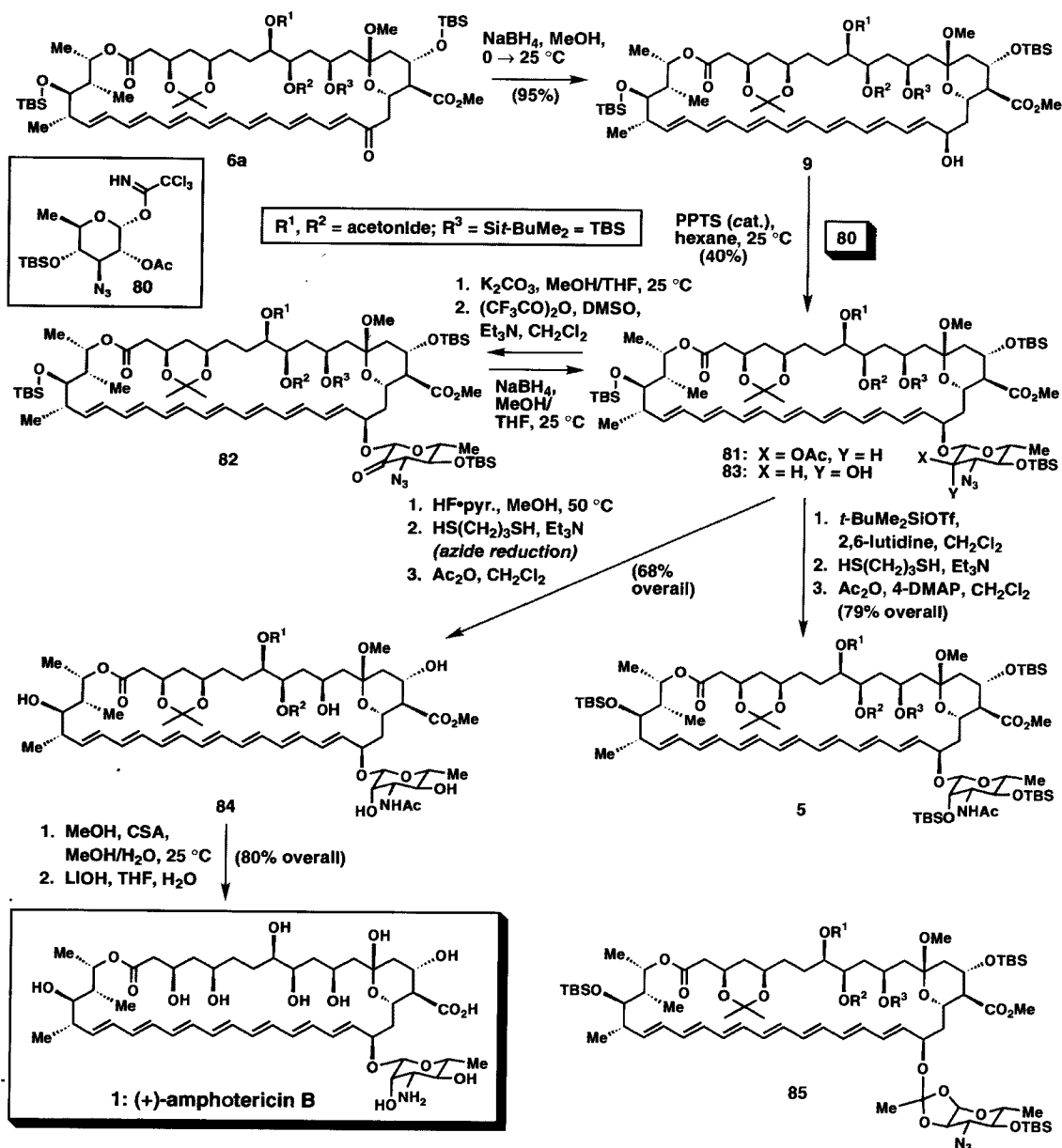
Scheme 17. Strategy for the stereocontrolled introduction of the mycosamine residue.

then envisioned to lead to amphotericin B (**1**). In the final scheme, a C-1 (anomeric) trichloroacetimidate²⁵ and a C-2 acetate were selected as the leaving and stereocontrolling groups, respectively, whereas an azido group (i.e. $\text{Y} = \text{N}_3$) was employed as a masked primary amine. Glycosyl donor **80** was, therefore, synthesized from the readily available²⁶ glucose derivative **75** through a multistep reaction sequence (see Scheme 18).

The final stages of the successful drive towards amphotericin B (**1**) are presented in Scheme 19. Thus, compound **9** is obtained stereoselectively by sodium borohydride reduction of heptaenone **6a** as previously described. The formation of the desired glycosidation product **81** could be achieved in dilute hexane solution in the presence of a catalytic amount PPTS. The by-product ortho ester **85** was also obtained in approximately an equimolar amount. Deacetylation of **81** at C-2, followed sequentially by oxidation and reduction leads, stereoselectively, to the desired hydroxy compound **83** via ketone **82**. The configuration of each of the two hydroxyl-bearing stereocenters generated by reduction of carbonyls as shown in Scheme 19 (**6** \rightarrow **9** and **82** \rightarrow **83**) were confirmed by conversion of **83** to amphotericin B derivative **5** and comparison with an



Scheme 18. Preparation of glycosyl donor **80**.



Scheme 19. Completion of the total synthesis of (+)-amphotericin B (1).

authentic sample derived from natural amphotericin B (**1**). The following sequence was utilized to achieve the final goal of arriving at amphotericin B (**1**). Fluoride-induced desilylation of **83**, followed sequentially by reduction of the azide to the amino group, hydrolysis of the acetonide and mixed-ketal groups, and alkaline hydrolysis, produces synthetic **1** via methyl ester **84**. Thus the total synthesis of (+)-amphotericin B (**1**) was accomplished.

24.4 Conclusion

The total synthesis of amphotericin B (**1**) described demonstrates the power of organic synthesis as it stood in the early 1980s. The ideas proposed within the original strategy were, for the most part, carried through to the completion of the synthesis. Noteworthy features of this strategy are: (i) the recognition and utilization of subtle symmetry elements in the target molecule by careful retrosynthetic analysis; (ii) the employment of the powerful Sharpless asymmetric epoxidation reaction; and (iii) the value of the chiral pool in providing enantiomerically pure starting materials for asymmetric synthesis. The Horner–Wadsworth–Emmons reaction emerged as perhaps the most useful carbon–carbon bond forming reaction in this synthesis, being utilized efficiently five times in the construction of the basic skeleton of amphoteronolide B (**2**). Particularly remarkable was the application of the intramolecular ketophosphonate–aldehyde version of this reaction to construct efficiently the 38-membered polyene macrolide ring of amphotericin B (**1**). The restriction of rotational freedom by the numerous substituents, double bonds, and rings on the backbone of the open-chain precursor proved to be instrumental in the success of this macroring-forming reaction. From this and other studies, it is clear that the intramolecular ketophosphonate–aldehyde condensation reaction is a highly effective method for the construction of macrorings and should, therefore, be placed high on the list of choices for such operations when applicable.

Other concepts successfully utilized in this synthesis include the stereocontrolled installation of hydroxyl-bearing stereocenters by reduction of carbonyl groups on either appropriately designed open-chain precursors or rings of common or large sizes. In particular, molecular modeling was found to be useful in the design and guidance of these studies. Additionally, a number of chemoselective reactions were observed in this sequence, demonstrating subtle conformational and/or functional group interactions in the rather complex intermediates involved.

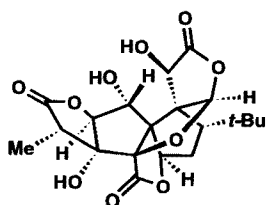
Finally, although ultimately successful, the glycosidation studies on amphotericin B (**1**) reemphasize the difficulties encountered in this important area of synthesis. Of course, the β -glycosidic bond linking the aglycon with the mycosamine, in combination with the

requisite 1,2-*cis* stereorelationship, presented a stringent test for contemporary glycosidation technology; however, the technology failed to provide a direct solution, and it was only after the design of an indirect strategy that the problem was finally solved. General, efficient, and stereoselective glycosidation methods will certainly have implications far beyond improving the present synthesis of amphotericin B (**1**).^{27,28}

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26. Eby, R.; Webster, K.T.; Schuerch, C. *Carbohydr. Res.* **1984**, *129*, 111.
27. For a separate synthesis of 19-dehydroamphoteronolide B, see: Kennedy, R.M.; Abiko, A.; Takemasa, T.; Okumoto, M.; Masamune, S. *Tetrahedron Lett.* **1988**, 451.
28. For some more recent degradation studies on amphotericin B, see: Driver, M.J.; MacLachlan, W.S.; MacPherson, D.T.; Readshaw, S.A. *J. Chem. Soc., Chem. Commun.* **1990**, 636.



1: ginkgolide B

25

E. J. Corey (1988)

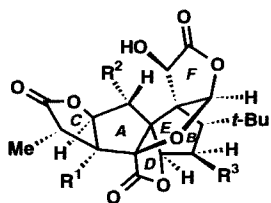
Ginkgolide B

25.1 Introduction

Fossil records reveal that the ginkgo tree, *Ginkgo biloba*, has existed on earth since the Liassic period, 280 million years ago, and that its population was greatest during the Jurassic period, 150 million years ago.¹ Also known as the maidenhair tree, *Ginkgo biloba* has probably existed on Earth longer than any other living tree.² The ginkgo tree is aptly referred to as a “living fossil”, or “fossil tree”, because it does not appear to have undergone any changes over the course of the last one million years.^{2,3} Although the order *ginkgoales* was once widespread throughout the world, all species except *Ginkgo biloba* are now extinct. Before the 18th century, the ginkgo tree was unknown outside the Orient; however, it is now widely distributed in Europe, America, and other continents.⁴

For centuries, the beneficial effects of crude extracts from the ginkgo tree were well known in China and India. In traditional Chinese medicine, a boiled-down extract of ginkgo leaves is inhaled to alleviate asthmatic symptoms, and, in India, ginkgo extracts constitute a key ingredient of *Soma*, a mystical liquid that is thought to increase life span.⁵ The Japanese know it as the *Itcho* tree and they frequently use its edible fruit, the ginkgo nut, in cooking.

The isolation of four terpenes from the bitter principles of *Ginkgo* by Furukawa in 1932⁶ marked an important advance in the quest for the identification of the active constituents of *Ginkgo* extracts. A second major milestone was reached in 1967 when Nakanishi and his group reported their extensive and brilliant studies which permitted the structures of these compounds to be fully defined.⁴ On the basis of spectroscopic data and chemical reactivity



ginkgolide B (1): $R^1 = OH$; $R^2 = OH$; $R^3 = H$
 ginkgolide A (2): $R^1 = OH$; $R^2 = H$; $R^3 = H$
 ginkgolide C (3): $R^1 = OH$; $R^2 = OH$; $R^3 = OH$
 ginkgolide M (4): $R^1 = H$; $R^2 = OH$; $R^3 = OH$

profiles, Nakanishi and his group correctly deduced the extremely complex structures of the four active principles of *Ginkgo* extracts and named them ginkgolides A (2), B (1), C (3), and M (4). At about the same time, Sakabe and his colleagues disclosed their X-ray crystallographic studies which confirmed the gross structures and absolute stereochemistry of the ginkgolides.⁷

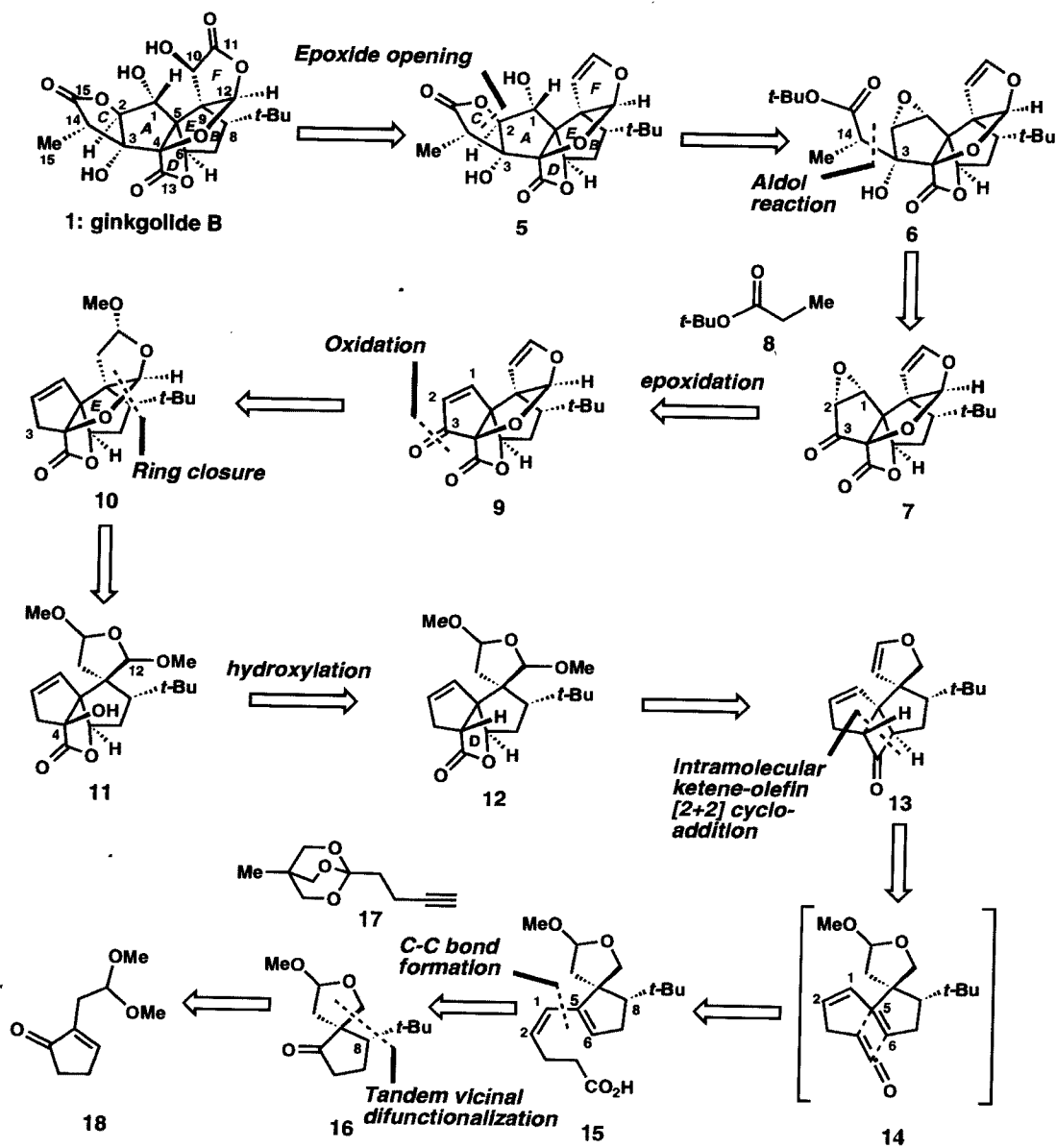
The unique cage structures of the ginkgolides comprise a central spiro[4.4]nonane carbon framework, three γ -lactone rings, one tetrahydrofuran ring, a *tert*-butyl group, and (for ginkgolide B) eleven stereogenic centers. The ginkgolides are truly impressive natural products and the *de novo* chemical synthesis of ginkgolide B (1) by E.J. Corey and his coworkers at Harvard stands as one of the great achievements of contemporary organic synthesis.⁸ The Corey synthesis of ginkgolide B (1) is a brilliant illustration of how sophisticated the science of organic synthesis has become, but at the same time it highlights gaps still existing in synthetic methodology, particularly with regard to selective oxidative functionalizations.⁹

In addition to its obvious architectural complexity, ginkgolide B (1) is also very complex from the stereochemical point of view. Of the twenty carbon atoms contained within ginkgolide B, eleven are asymmetrically substituted. Rings A and E are sites of an unusually heavy concentration of asymmetry; all five carbon atoms in the A-ring of ginkgolide B are tetrahedral and unsymmetrically substituted, and the same is true for the four carbon atoms of ring E. Moreover, the B-ring of 1 accommodates a consecutive chain of four stereogenic centers, two of which are quaternary.

The *tert*-butyl group attached to ring B of ginkgolide B (1) is a highly unusual structural feature. In fact, before 1967 there was no precedent for the presence of a *tert*-butyl group in natural products.⁴ A subtle and brilliant feature of Corey's design is the early introduction of this substituent. The disposition of the B-ring *tert*-butyl group is used to control the formation of three stereogenic centers. The key features of Corey's synthesis of ginkgolide B (1) are outlined retrosynthetically in Scheme 1.

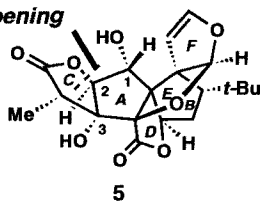
25.2 Retrosynthetic Analysis and Strategy

Before significant, structurally simplifying transforms can be applied to 1, it is first necessary to conceal the reactive functionality contained within ring F of ginkgolide B. Intermediate 5, the product of the first retrosynthetic maneuver, contains a stable ring F surrogate which no longer possesses electrophilic potential. The ring F enol ether in 5 is, however, amenable to a straightforward sequence of functional group transformations to secure the formation of the F-ring of ginkgolide B. Of the six five-membered rings that constitute the cage framework of ginkgolide B, the

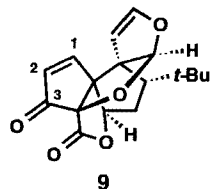
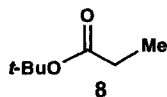
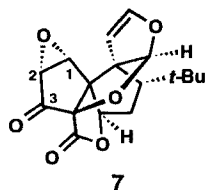
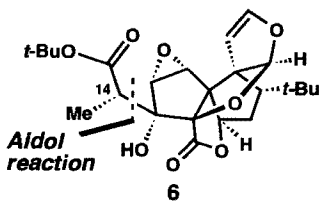


Scheme 1. Retrosynthetic analysis of ginkgolide B (1).

Epoxide opening



Aldol reaction



γ -lactone representing ring C of the natural product is joined to only one ring. Ring C can thus be regarded as a substituent appended to ring A; it possesses an electrophilic carbonyl group that could potentially react in undesirable ways, and it is therefore necessary to defer its introduction to a late stage in the synthesis. Included within the C–A substructure of intermediate **5** is a hydroxyl group at C-1 and a proximal γ -lactone ring at carbons 2 and 3. Together, these structural elements constitute the retron for an oxylactonization transform,¹⁰ which reveals intermediate **6** as a potential precursor. Under suitably acidic conditions, and in the forward sense, cleavage of the *tert*-butyl ester in **6**, followed by intramolecular opening of the oxirane ring, could conceivably give intermediate **5**. Of course the β -hydroxy ester in **6** is itself a retron for a structurally simplifying aldol transform. Thus, cleavage of the indicated carbon–carbon bond in **6** leads back to epoxy ketone **7** and *tert*-butyl propionate **8**. A straightforward aldol condensation between the (*Z*)-enolate derived from **8** and the electrophilic A-ring ketone carbonyl in **7** would appear to be particularly well suited for the formation of this key carbon–carbon bond and the creation of functionality that will eventually be present in ginkgolide B (**1**).

At this juncture, it is necessary to address some very important stereochemical issues. It is difficult to predict, *a priori*, which ketone diastereoface in **7** would experience attack by a propionate enolate. However, it seems reasonable to suppose that by virtue of the α -face disposition of the oxirane ring in **7**, a steric approach controlled addition of the enolate derived from **8** could very well lead to the predominant formation of the desired aldol adduct. It is also important to recognize that during the course of the addition of the enolate of **8** to the ketone carbonyl in **7**, a trigonal enolate carbon atom is converted into a tetrahedral carbon atom. The geometry of the enolate determines the configuration of the tetrahedral carbon atom at position 14 in **6**, and the inherent tendency to minimize destabilizing nonbonding interactions in the transition state determines which enolate enantioface will participate in the aldol addition reaction. The aldol condensation process is *stereospecific* with respect to the enolate, and, to achieve the selective formation of **6**, it is imperative that **8** be converted into a *Z*-propionate enolate. Fortunately, the pioneering studies of Ireland and his coworkers demonstrate that it is possible to define the geometry of ester enolates simply by controlling the nature of the solvent for the enolization reaction.¹¹

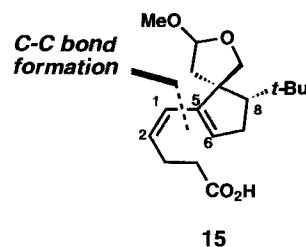
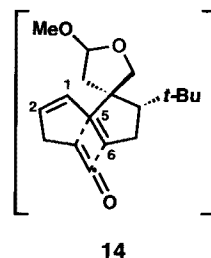
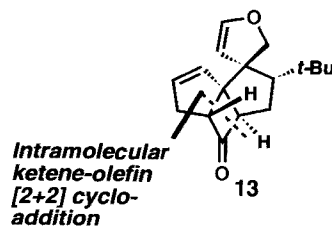
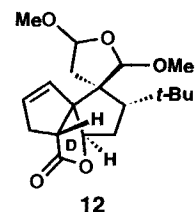
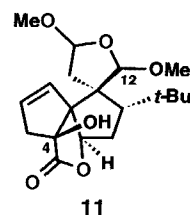
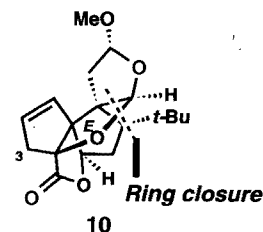
The next logical target for retrosynthetic disassembly is the oxirane ring in **7**. The oxygen atom of the epoxide will eventually be expressed in the form of a C-1 hydroxyl group in ginkgolide B and it could conceivably be introduced through a straightforward epoxidation of the enone carbon–carbon double bond in **9**. It is noteworthy that the combination of oxylactonization, aldol, and epoxidation transforms allows for dramatic structural and stereochemical simplification (**5** \rightarrow **6** \rightarrow **7** \rightarrow **9**).

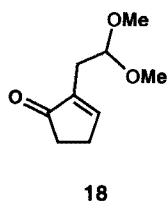
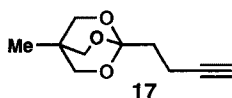
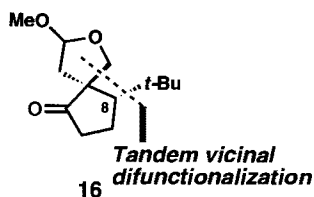
The relationship between **9** and its predecessor **10** is close. Oxidation of the allylic C-3 methylene group in **10** and elimination of the methoxy group could furnish enone **9**. Retrosynthetic disassembly of ring E in **10** furnishes tertiary alcohol **11** as a viable precursor. That treatment of **11** with a catalytic amount of acid will induce the formation of a transient oxonium ion at C-12 which is then intercepted by the appropriately placed C-4 tertiary hydroxyl group is a very reasonable proposition. As we will see, the introduction of the requisite C-4 hydroxyl group is straightforward from intermediate **12**.

We are now in a position to address the origin of the γ -lactone ring D. The Baeyer–Villiger oxidation is a very valuable reaction in organic synthesis;¹² it allows cyclic and acyclic ketones to be oxidized in a regioselective and stereospecific manner to lactones and esters, respectively. When applied to cyclic ketones, the Baeyer–Villiger oxidation expands the size of the ring by one atom. Application of the Baeyer–Villiger transform to **12** furnishes cyclobutanone **13** as a potential precursor. In the structural context of **13**, it is difficult to predict, *a priori*, the regiochemical course of a Baeyer–Villiger oxidation of the cyclobutanone ring. It was anticipated, however, that the desired γ -lactone ring could be formed selectively through a judicious choice of reagents and reaction conditions.

A central and elegant feature of Corey's synthesis is the use of the spiro[4.4]nonane framework, formed from rings A and B, as a template upon which rings C, D, and E are assembled. The angularly fused cyclobutanone **13** is a key synthetic intermediate; although it is a complicated molecular assembly, it possesses the structural prerequisite for the dramatically simplifying intramolecular ketene–olefin [2+2] cycloaddition transform. Thus, retrosynthetic disassembly of **13** by cleavage of the indicated carbon–carbon bonds leads back to ketene olefin **14**. The intermediacy of **14** would be brief; once formed, it should participate in a facile intramolecular [2+2] cycloaddition reaction¹³ to give intermediate **13**. Ketene olefin **14** could be obtained in a straightforward manner from carboxylic acid **15**. In the forward sense, intermediate **15** could be converted into the corresponding acid chloride and subsequently exposed to an amine base in refluxing toluene. Under these conditions, the acid chloride derived from **15** should undergo conversion into intermediate **13** through the intermediacy of the putative ketene olefin **14**. Thus, in two operationally straightforward steps, a complex, angularly fused tetracyclic framework could be fashioned from a comparatively simple bicyclic carboxylic acid. If viable, this reaction sequence could create two new rings and three key stereocenters.

It is instructive to note that the intramolecular [2+2] cycloaddition process should benefit from the presence of the *cis* C1–C2 double bond in **14**. Indeed, the *cis* C1–C2 double bond is expected to facilitate the key [2+2] cycloaddition event by bringing into proximity the reactive ketene moiety and the C5–C6 olefin and by





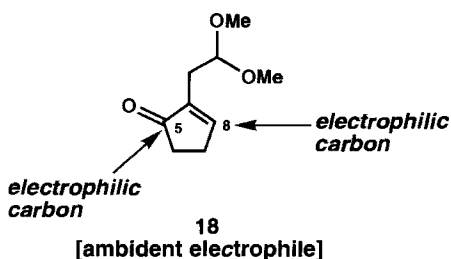
reducing rotational freedom of the tether linking the two reacting groups (see intermediate **14**). Of course, the unsaturation between positions 1 and 2 also provides for the eventual elaboration of ring C and the secondary hydroxyl group at C-1 in ginkgolide B.

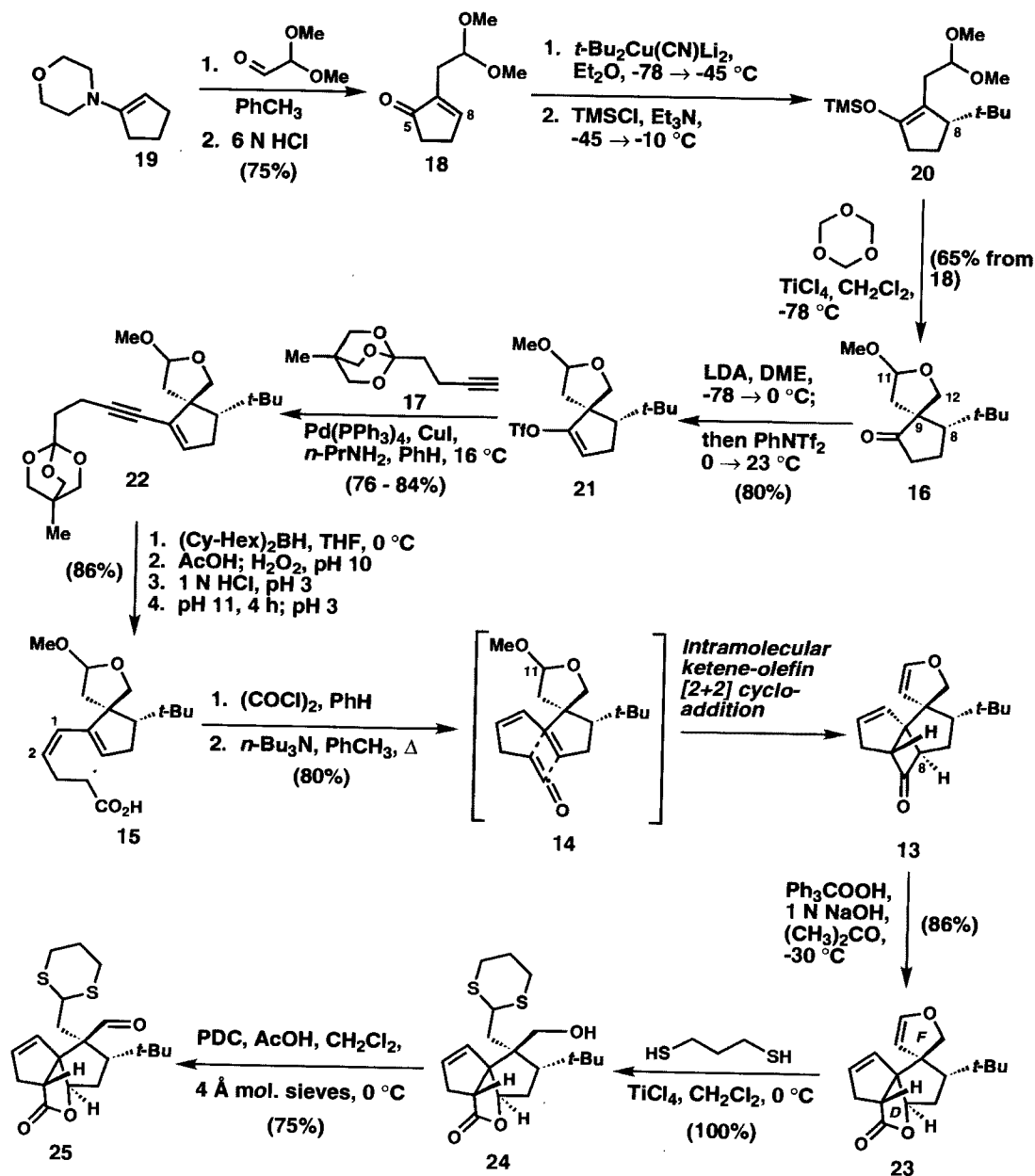
Through the application of powerful bond-forming strategies, the intimidating structural and stereochemical complexity of ginkgolide B (**1**) has been significantly simplified. The synthetic problem is now reduced to the preparation of intermediate **15**, a spirocyclic molecule harboring only two asymmetric carbon atoms. Retrosynthetic cleavage of the indicated carbon-carbon bond in **15** furnishes intermediates **16** and **17** as potential precursors. Removal of the indicated appendages from **16** furnishes achiral enone **18**, a simple and readily available starting material. During the course of the conversion of **18** into **16**, the *tert*-butyl group at position 8 is introduced. At the outset of this synthesis, it was anticipated that the bulky *tert*-butyl substituent at C-8 could, by exerting control over the conformation of intermediate **14**, direct the stereochemical course of the key intramolecular ketene-olefin [2+2] cycloaddition reaction.

25.3 Total Synthesis

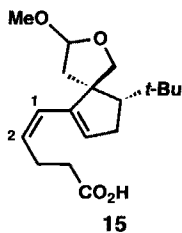
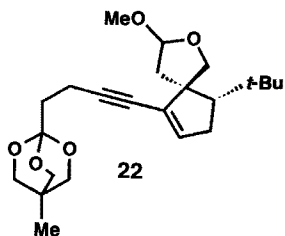
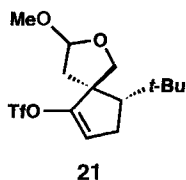
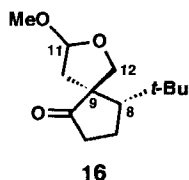
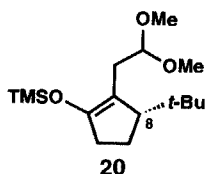
Corey's elegant synthesis of ginkgolide B (**1**) commences with the reaction of the morpholine enamine **19**, derived from cyclopentanone, with dimethoxyacetaldehyde in toluene (see Scheme 2). Treatment of the stereoisomeric condensation products with 6 N HCl accomplishes reconstitution of the ketone carbonyl group, dehydration of the secondary alcohol, and olefin isomerization to give intermediate **18** in an overall yield of 75 %. The stability of the dimethyl acetal protecting group under these conditions is noteworthy. This simple two-step reaction sequence employs readily accessible starting materials and permits intermediate **18** to be prepared in multigram quantities. Enone **18** is an ambident electrophile; it is endowed with electrophilic potential at carbons 5 and 8 and it can react with nucleophilic species at one or both of these sites. A most useful consequence of a 1,4-, or conjugate, addition to an α,β -unsaturated carbonyl derivative is the formation of an enolate that can be employed as a nucleophile in a subsequent reaction. In principle, the conjugate addition and subsequent functionalization of the enolate carbon atom can be carried out in one pot. Also known as a tandem vicinal difunctionalization reaction, this process can create two new vicinal carbon-carbon bonds and has emerged as a powerful tool in organic synthesis.¹⁴

In this synthesis, a tandem vicinal difunctionalization of enone **18** provides an exceedingly simple solution to the task of synthesizing spirocyclic intermediate **16**. When **18** is treated with the organocuprate reagent, *t*-Bu₂Cu(CN)Li₂, a smooth 1,4- or Michael ad-





Scheme 2. Synthesis of intermediate 25.



dition takes place to give, after silylation of the enolate oxygen atom with trimethylsilyl chloride, intermediate **20**. This straightforward reaction sequence accomplishes the introduction of the requisite *tert*-butyl substituent at C-8 and the formation of a latent nucleophilic TMS enol ether. When a cold (-78°C) solution of **20** in methylene chloride is treated with 1,3,5-trioxane and titanium(IV) chloride, intermediate **16** is formed in an overall yield of 65 % from **18**. The orientation of the bulky *tert*-butyl substituent in **20** shields one of the two diastereotopic faces of the silyl enol ether and induces the Mukaiyama condensation¹⁵ to proceed across the more accessible face to give, exclusively, intermediate **16** as the kinetic product. The absence of an NOE between the C-8 *tert*-butyl group and the methylene protons at C-12 was used to provide support for the assignment of stereochemistry in **16**. Although **16** is obtained as a 2:1 mixture of diastereoisomers, epimeric at C-11, correct relative stereochemistry at positions 8 and 9 is secured by this reaction sequence. The formation of a mixture of C-11 epimers is ultimately of no consequence because this stereocenter is destroyed later in the synthesis. It is instructive to note that the facile, titanium(IV) chloride-promoted formation of the mixed cyclic acetal prevents the kinetic product from equilibrating through a retroaldol/aldol process.^{8b}

Concealed within spirocyclic intermediate **16** are rings B and F of ginkgolide B. Intermediate **16** is readily formed in two steps from a readily available starting material and it contains a strategically placed ketone carbonyl group which provides several options for further advance. A particularly straightforward route to **15** includes the conversion of ketone **16** into enol triflate **21** by means of McMurry's protocol.¹⁶ Thus, enolization of **16** with LDA in dimethoxyethane at -78°C followed by triflation of the enolate oxygen atom with *N*-phenyltrifluoromethanesulfonimide furnishes enol triflate **21** in a yield of 80 %.

A synthetically useful virtue of enol triflates is that they are amenable to palladium-catalyzed carbon-carbon bond-forming reactions under mild conditions. When a solution of enol triflate **21** and tetrakis(triphenylphosphine)palladium(0) in benzene is treated with a mixture of terminal alkyne **17**, *n*-propylamine, and cuprous iodide,¹⁷ intermediate **22** is formed in 76–84 % yield. Although a partial hydrogenation of the alkyne in **22** could conceivably secure the formation of the *cis* C1–C2 olefin, a chemoselective hydroboration/protonation sequence was found to be a much more reliable and suitable alternative. Thus, sequential hydroboration of the alkyne **22** with dicyclohexylborane, protonolysis, oxidative work-up, and hydrolysis of the oxabicyclo[2.2.2]octyl ester protecting group gives dienic carboxylic acid **15** in a yield of 86 % from **22**.

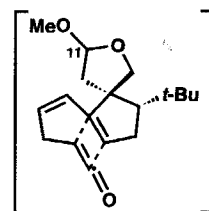
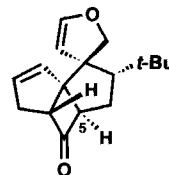
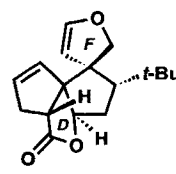
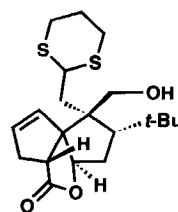
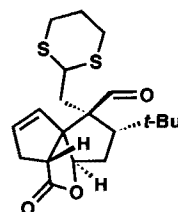
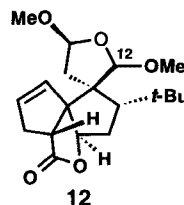
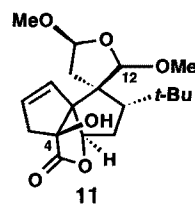
During the course of the conversion of intermediate **18** into intermediate **16**, the imposing *tert*-butyl substituent at C-8 guides the formation of the adjacent stereocenter at C-9 and it is now called upon to guide, or at least influence in a favorable way, the stereo-

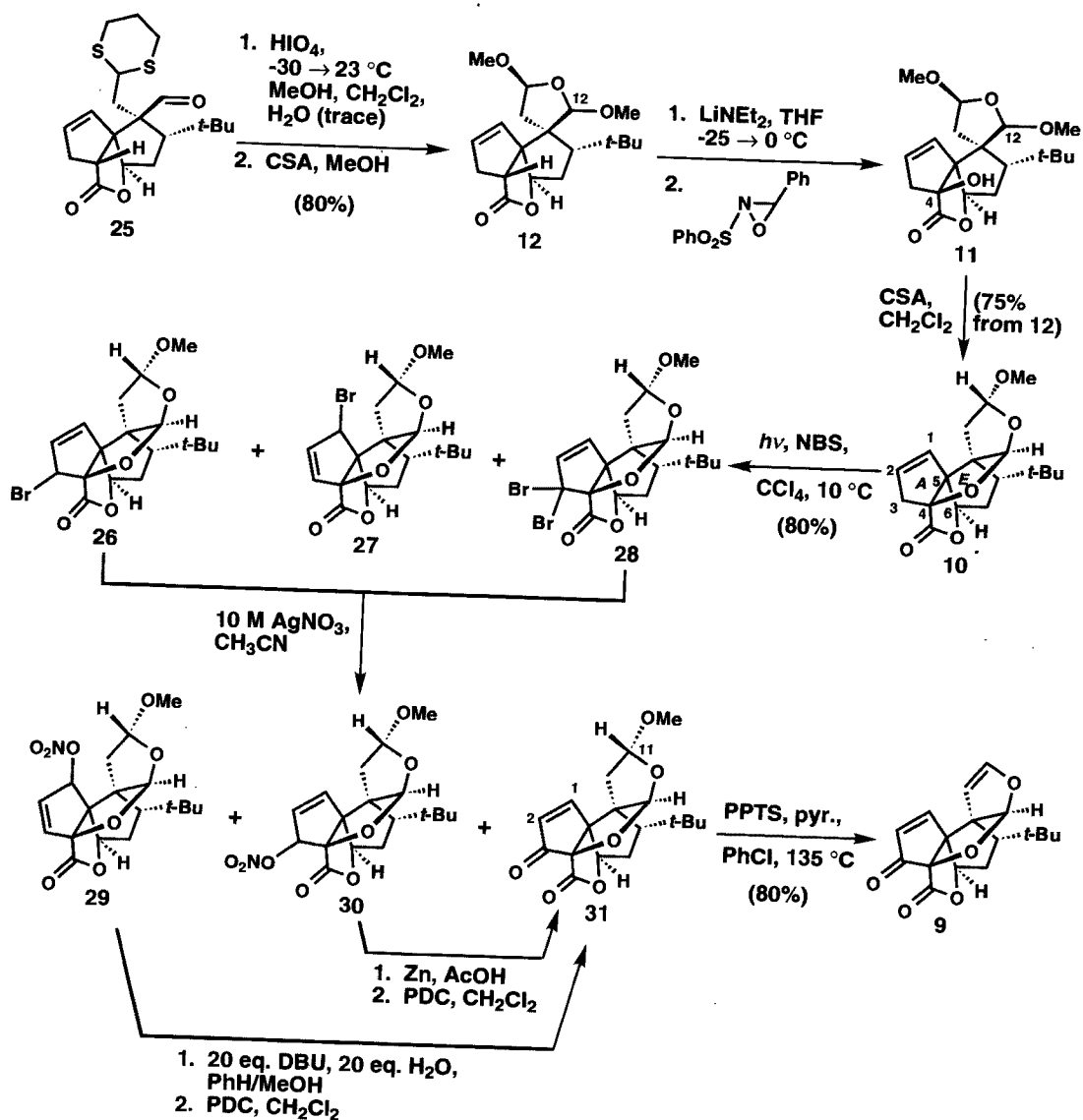
chemical course of the crucial intramolecular [2+2] cycloaddition event. When the acid chloride derived from the action of oxalyl chloride on carboxylic acid **15** is treated with tri-*n*-butylamine in refluxing toluene, it undergoes smooth conversion to tetracycle **13** via ketene **14**. It is noteworthy that this intramolecular ketene-olefin [2+2] cycloaddition reaction is stereospecific, and it furnishes the architecturally complex intermediate **13** in an excellent yield of 80%. Interestingly, at some point during the course of the cycloaddition event, the tri-*n*-butylamine hydrochloride that is formed in this reaction promotes the elimination of the anomeric C-11 methoxy group. This fortuitous event proved very useful in the final stages of the synthesis when it was necessary to remove the anomeric methoxy group.

An important feature of Corey's design is the recognition that the γ -lactone D-ring of ginkgolide B could conceivably be derived from the cyclobutanone ring in **13**. A Baeyer-Villiger oxidation¹² of **13**, with retention of configuration at C-6, would appear to be particularly well-suited for this task. It is likely that the action of an electron-deficient oxidant, such as *m*CPBA, on **13** could achieve the oxidation of the cyclobutanone ring to the corresponding γ -lactone ring. However, in addition to an oxidizable cyclobutanone ring, intermediate **13** possesses two π bonds, one of which is appreciably electron rich, and it is likely that one or both of these sites would compete with the cyclobutanone ring for reaction with *m*CPBA. Fortunately, the desired oxidation could be achieved with a nucleophilic oxidant. Treatment of **13** with triphenylmethyl (trityl) hydroperoxide and sodium hydroxide in acetone at -30°C furnishes intermediate **23**, exclusively, in a yield of 86%. It is noteworthy that the use of less bulky oxidants, such as basic hydrogen peroxide, led to the formation of a 1:1 mixture of regioisomeric γ -lactones.

To create a setting favorable for the formation of the E-ring of ginkgolide B, it is first necessary to modify the reactivity potential of ring F in **23**. Exposure of a solution of **23** in methylene chloride to 1,3-propanedithiol and titanium(IV) chloride at 0°C results in the formation of dithiane **24** in quantitative yield. Oxidation of the primary alcohol with PDC in the presence of acetic acid gives aldehyde **25** in a yield of 75%.

When a solution of **25** in a 1:1 mixture of methanol and methylene chloride is exposed to periodic acid, the dithiane group is cleaved oxidatively to give, after treatment of the crude product with camphorsulfonic acid (CSA) in methanol, bisacetal **12** as a 2:1 mixture of C-12 anomers in a yield of 80% (Scheme 3). Although the conversion of **12** into **10** could be carried out on the mixture of anomers, it was found to be more convenient to carry each isomer forward separately. When **12** is treated with lithium diethylamide, the methine hydrogen adjacent to the lactone carbonyl is removed as a proton to give an enolate which is then oxidized in a completely diastereoselective fashion with Davis's oxaziridine¹⁸ to afford **11**.

**14****13****23****24****25****12****11**

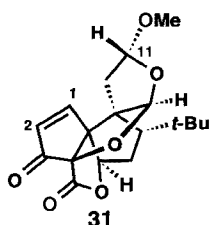


Scheme 3. Synthesis of intermediate 9.

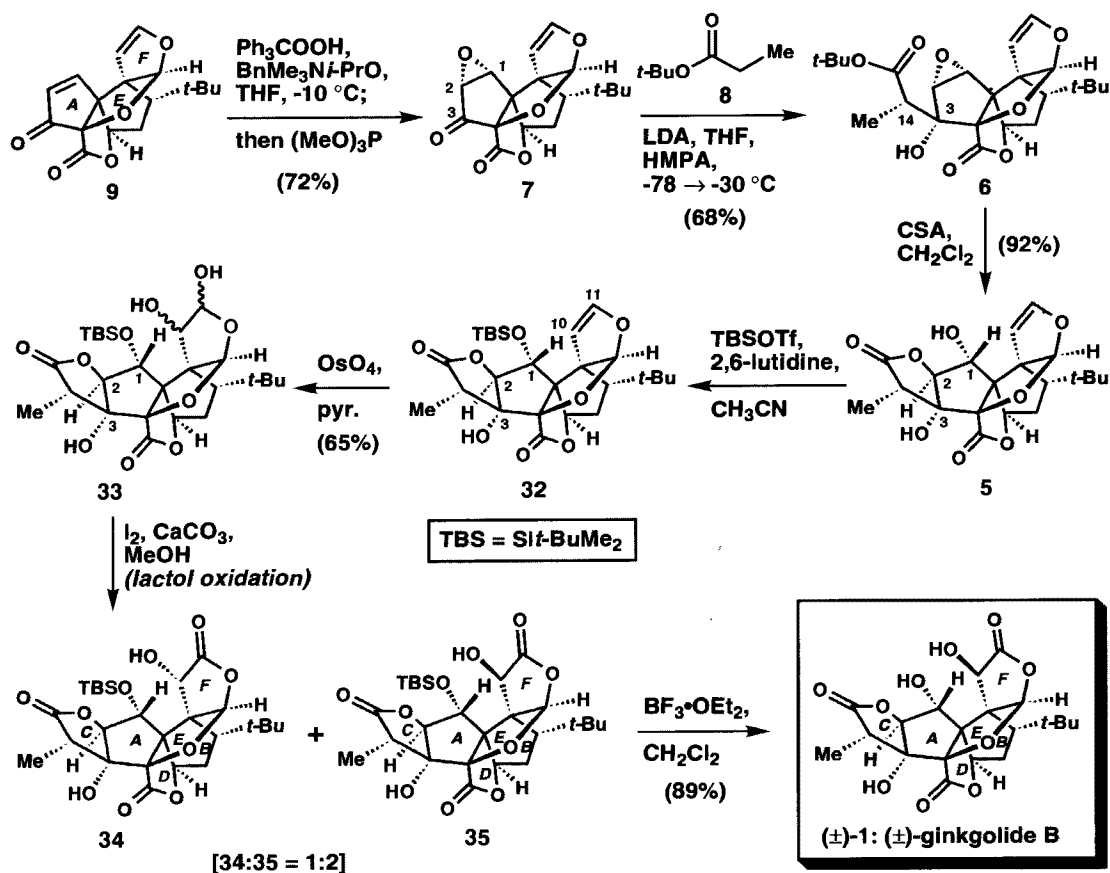
The hydroxylation reaction, whose stereochemical course is controlled by the strong inherent preference for the formation of a *cis*-fused 5,5 ring system, creates a molecule which would appear to be well suited for an intramolecular etherification reaction to give ring E of ginkgolide B (**1**). Indeed, when a solution of **11** in methylene chloride is exposed to camphorsulfonic acid (CSA), a smooth cyclization reaction takes place to give intermediate **10** in an overall yield of 75 % from **12**. The action of CSA on **11** produces a transient oxonium ion at C-12 which is intercepted intramolecularly by the proximal hydroxyl group at C-4.

The synthesis of pentacycle **10** with its six contiguous asymmetric carbon atoms is, in itself, a noteworthy achievement. That six grams of this substance have been prepared is striking testimony to the remarkable efficiency of Corey's strategy. In order to achieve the formation of the sixth and final five-membered ring of ginkgolide B, it is necessary to modify ring A in intermediate **10**. As in the case of the *tert*-butyl group at C-8, the C1–C2 olefin plays several important roles in this synthesis: (a) it facilitates the intramolecular [2+2] cycloaddition by bringing the ketene and the C5–C6 olefin into proximity and by imparting conformational rigidity to the tether linking the two reacting groups; (b) it labilizes the two allylic carbon–hydrogen bonds at C-3 so that this carbon can be functionalized; and (c) it provides a suitable platform upon which requisite functionality can be introduced. When intermediate **10** is irradiated in the presence of *N*-bromosuccinimide, a 6:3:1 mixture of allylic bromides (**26**, **27**, and **28**) is produced in a combined yield of 80 %. Treatment of this mixture with 10 M AgNO₃ in acetonitrile gives enone **31**, a product formed from dibromide **28**, and the two regioisomeric allylic nitrate esters **29** and **30**. After separation and characterization, the two allylic nitrate esters **29** and **30** could be converted independently into the same allylic alcohol and then into enone **31** through the sequence of reactions illustrated in Scheme 3. From intermediate **10**, this sequence of reactions furnishes enone **31** in a yield of 50 %.

During the planning stages of this synthesis, the task of achieving an allylic oxidation of intermediate **10** was probably not regarded as being too difficult. After all, oxidations of allylic methylene groups are routinely carried out in organic synthesis. Unfortunately, however, the seemingly straightforward oxidation of **10** to **31** proved to be the most difficult transformation in the synthesis. Many of the more conventional oxidation protocols were examined and were found to be unsuccessful.^{8b} This example illuminates a weakness still existing in organic synthesis methodology for C–H activation and it emphasizes the importance of basic research in organic synthesis. Although the science of assembling complex organic molecules has already reached an impressive level of sophistication, deficiencies that obviously still exist in synthetic methodology must be remedied before organic synthesis can universally be regarded as a practical endeavor.¹⁹



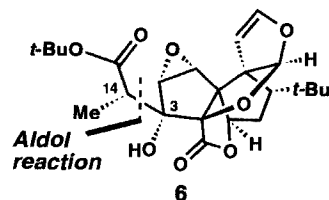
Now that the allylic oxidation problem has been solved adequately, the next task includes the introduction of the epoxide at C-1 and C-2. When a solution of **31** and pyridinium *para*-toluenesulfonate in chlorobenzene is heated to 135 °C, the anomeric methoxy group at C-11 is eliminated to give intermediate **9** in 80 % yield. After some careful experimentation, it was found that epoxy ketone **7** forms smoothly when enone **9** is treated with triphenylmethyl hydroperoxide and benzyltrimethylammonium isopropoxide (see Scheme 4). In this reaction, the bulky oxidant adds across the more accessible convex face of the carbon framework defined by rings A, E, and F, and leads to the formation of **7** as the only stereoisomer in a yield of 72 %.



Scheme 4. Synthesis of (±)-ginkgolide B [(±)-1].

The oxirane ring in **7** is an essential structural feature. First, its oxygen atom, which is destined to rest in ginkgolide B in the form of a C-1 hydroxyl group, is positioned correctly in space. Second, its orientation in space should shield the α -face of the C-3 ketone carbonyl in **7**, thereby favoring a β -face addition of a propionate enolate. Third, its inherent electrophilic character could, in a suitable setting, enable the formation of the sixth and final ring of ginkgolide B. When intermediate **7** is exposed to the enolate anion derived from the action of LDA on *tert*-butyl propionate **8** in a mixture of THF and HMPA, an 8:1 mixture of diastereoisomeric aldol adducts is formed in a yield of 68 %. Fortunately, the desired aldol adduct, intermediate **6**, is produced in larger relative measure and it is equally significant that the relative stereochemical relationship between the two newly created stereocenters at C-14 and C-3 in **6** is identical to that found in ginkgolide B (**1**).

We have now reached a pivotal stage in the synthesis. We have retraced the elegant sequences of reactions that have led to the synthesis of the architecturally and stereochemically complex pentacyclic intermediate **6**. The intermolecular aldol condensation that we have just witnessed accomplishes the simultaneous formation of a key bond between carbons 3 and 14 and the introduction of two key stereogenic centers. An additional consequence of the aldol condensation, which has important strategic implications, is that the *tert*-butyl ester and epoxide groups are forced into neighboring regions of space. When a solution of **6** in methylene chloride is treated with camphorsulfonic acid, a smooth lactonization reaction takes place with concomitant opening of the oxirane ring to give intermediate **5** in an excellent yield of 92 %. During the course of the lactonization reaction, a new carbon–oxygen bond is created at C-2 with complete inversion of stereochemistry. The introduction of the sixth and final five-membered ring of ginkgolide B is now accomplished, and the completion of the total synthesis only requires a few straightforward functional group manipulations on intermediate **5**. After silylation of the C-1 hydroxyl group in **5** (to afford **32**), dihydroxylation of the C10–C11 olefin furnishes a stereoisomeric mixture of diols **33** which gives, after selective oxidation of the lactol, a 1:2 mixture of α -hydroxy lactones **34** and **35**. Treatment of **35** with an excess of boron trifluoride etherate effects desilylation of the C-1 secondary hydroxyl group and furnishes (\pm)-ginkgolide B [(\pm)-**1**] in a yield of 89 %. The total synthesis of ginkgolide B is now complete.²⁰



25.4 Conclusion

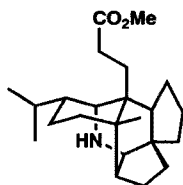
Of the many interesting and productive stages in Corey's synthesis of ginkgolide B, it is the intramolecular ketene–olefin [2+2] cycloaddition step that is perhaps the most impressive (see **14** \rightarrow **13**). The conversion of **14** to **13** is attended by the formation

of two new rings and three contiguous stereocenters. The rigid spirocyclic nucleus constructed in this step represents rings A and B, and the cyclobutane ring serves as a suitable progenitor for the D-ring of ginkgolide B. The early introduction of the target molecule's encumbered *tert*-butyl substituent affixed to C-8 in intermediate **20** guides the formation of the adjacent quaternary stereocenter at C-9, and it directs the stereochemical course of the crucial [2+2] cycloaddition step.

Corey's solution to the intimidating structural and stereochemical complexities of ginkgolide B features an impressive collection of powerful bond-forming strategies. The first total synthesis of ginkgolide B by the Corey group is a major achievement of contemporary organic synthesis.

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19. For an interesting discussion, see: Heathcock, C. H. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 665.
20. Soon after the disclosure of the total synthesis of (\pm)-ginkgolide B, (see ref. 8a) Corey reported a concise, enantioselective synthesis of tetracyclic lactone **23**, see: Corey, E. J.; Gava, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201. Thus, in principle, ginkgolide B could be synthesized in its naturally occurring enantiomeric form.



1: methyl homosecodaphniphyllate

C. H. Heathcock (1988)

Methyl Homosecodaphniphyllate

26.1 Introduction

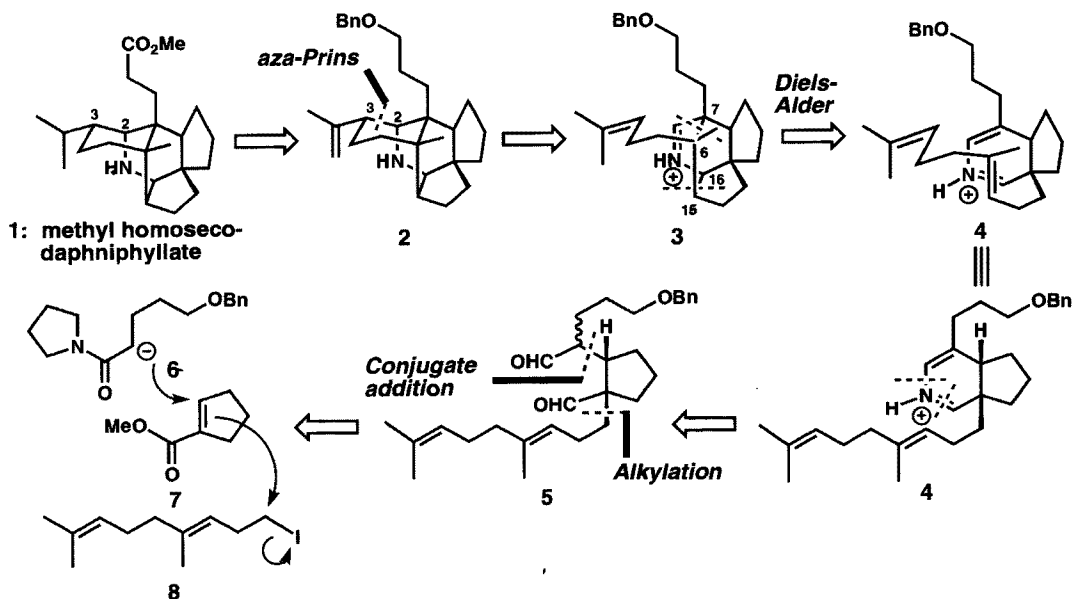
The oriental tree, Yuzuriha (*Daphniphyllum macropodum*), is the source of an impressive family of alkaloids that are derived biosynthetically from squalene. For centuries, extracts from the bark and leaves of Yuzuriha have been used for the treatment of asthma, but it was not until the 1960s that modern methods of structural analysis permitted the elucidation of the intricate structures of several members of this family. The structure of methyl homosecodaphniphyllate (**1**) was revealed by an X-ray crystallographic analysis and was disclosed in 1971 by Sasaki and Hirata.¹ The pentacyclic framework of **1** accommodates eight contiguous asymmetric carbon atoms, three of which are fully substituted (i.e. quaternary). In spite of its complex structure, an exceedingly concise and elegant total synthesis of methyl homosecodaphniphyllate was achieved by Heathcock and coworkers at U.C. Berkeley.² This elegant strategy evolved from considerations of a plausible biosynthetic path from squalene to the pentacyclic skeleton of **1**.³ Its general features are outlined retrosynthetically below.

26.2 Retrosynthetic Analysis and Strategy

Guided by the desire to preserve the squalene chain for as long as possible, Heathcock's strategy for the synthesis of methyl homosecodaphniphyllate (**1**) defers the formation of a carbon-carbon bond between positions 2 and 3 to a late stage in the synthesis

(Scheme 1). Introduction of a π bond into the molecular structure of **1** furnishes homoallylic amine **2** and satisfies the structural prerequisite for an aza-Prins transform.⁴ Thus, disconnection of the bond between C-2 and C-3 affords intermediate **3** as a viable precursor. In the forward sense, a cation π -type cyclization, or aza-Prins reaction, could achieve the formation of the C2–C3 bond and complete the assembly of the complex pentacyclic skeleton of the target molecule (**1**). Reduction of the residual π bond in **2**, hydrogenolysis of the benzyl ether, and adjustment of the oxidation state at the side-chain terminus would then complete the synthesis of **1**.

Although intermediate **3** is still an imposing molecular assembly, it can be dismantled in a way that greatly simplifies the synthetic problem. Thus, retrosynthetic cleavage of the C6–C7 and C15–C16 bonds leads back to intermediate **4**. In a single event, an intramolecular Diels–Alder reaction between the protonated form of the azadiene moiety in **4** and the trisubstituted olefin four atoms away could accomplish the formation of two key carbon–carbon bonds and two new rings. Azadiene **4** could conceivably be formed in a very straightforward manner from the action of ammonia on dialdehyde **5**. An elegant and distinguishing feature of this synthesis is the recognition that all of the carbon atoms of intermediate **5** could be introduced in one triply convergent step through a tandem Michael addition/enolate alkylation reaction employing intermediates **6**, **7**, and **8**. In fact, with the exception of the carbomethoxy methyl group, this productive, three-component coupling process



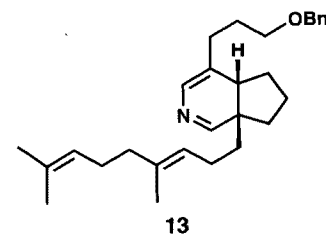
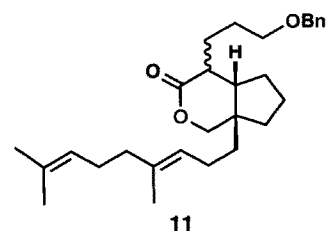
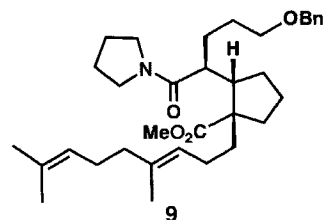
Scheme 1. Retrosynthetic analysis of methyl homosecodaphniphyllate (**1**).

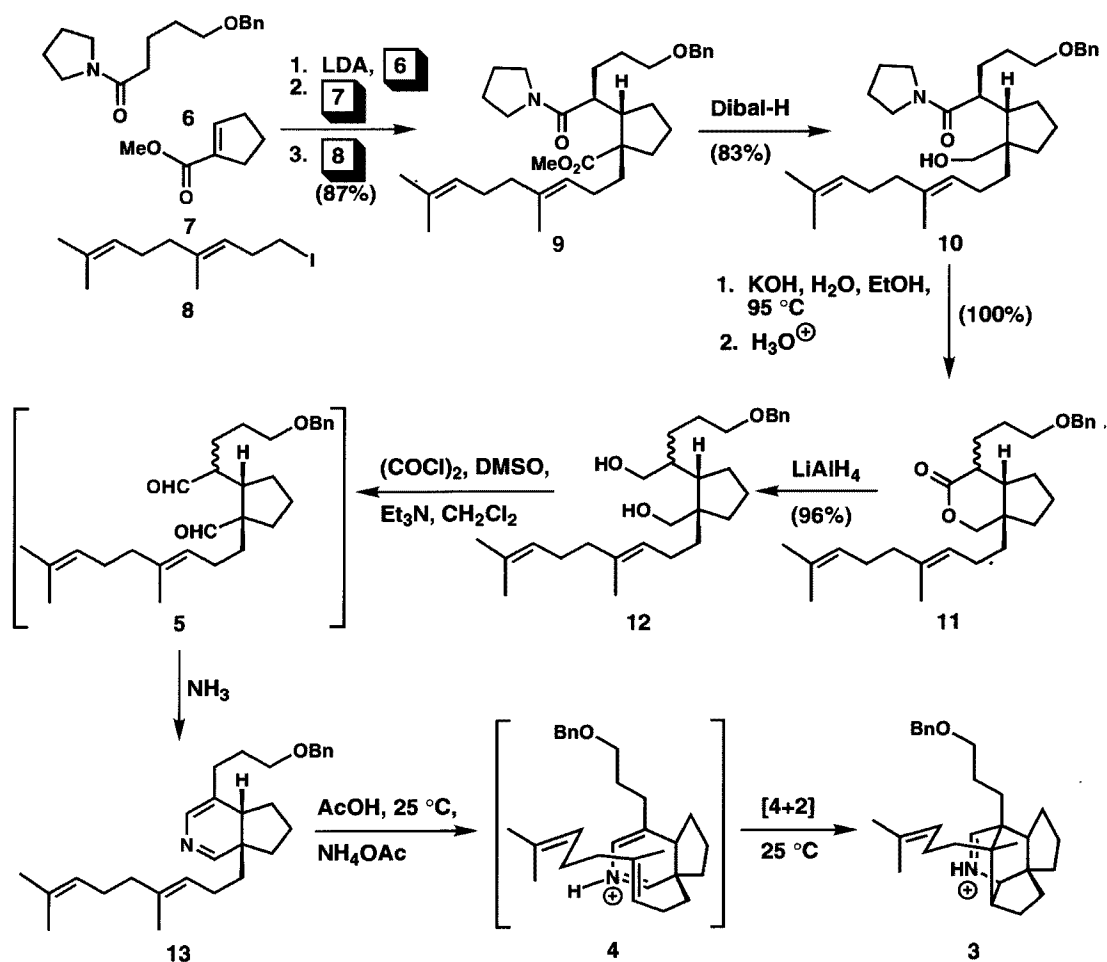
introduces all of the carbon atoms of the natural product. It was anticipated that the enolate anion derived from **6** should react selectively with the electrophilic β -carbon atom of Michael acceptor **7** to afford a new enolate, which can then participate in a C-alkylation reaction with homogeranyl iodide **8**. For steric reasons, the relative disposition of the two side-chain appendages (see intermediate **5**) should be *trans*. The synthetic strategy derived from this analysis was smoothly executed as described below.

26.3 Total Synthesis

When a cold (-78°C) solution of the lithium enolate derived from amide **6** is treated successively with α,β -unsaturated ester **7** and homogeranyl iodide **8**, intermediate **9** is produced in 87% yield (see Scheme 2). All of the carbon atoms that will constitute the complex pentacyclic framework of **1** are introduced in this one-pot operation. After some careful experimentation, a three-step reaction sequence was found to be necessary to accomplish the conversion of both the amide and methyl ester functions to aldehyde groups. Thus, a complete reduction of the methyl ester with diisobutylaluminum hydride (Dibal-H) furnishes hydroxy amide **10** which is then hydrolyzed with potassium hydroxide in aqueous ethanol. After acidification of the saponification mixture, a 1:1 mixture of diastereomeric δ -lactones **11** is obtained in quantitative yield. Under the harsh conditions required to achieve the hydrolysis of the amide in **10**, the stereogenic center bearing the benzyloxypentyl side chain epimerized. Nevertheless, this seemingly unfortunate circumstance is ultimately of no consequence because this carbon will eventually become part of the planar azadiene.

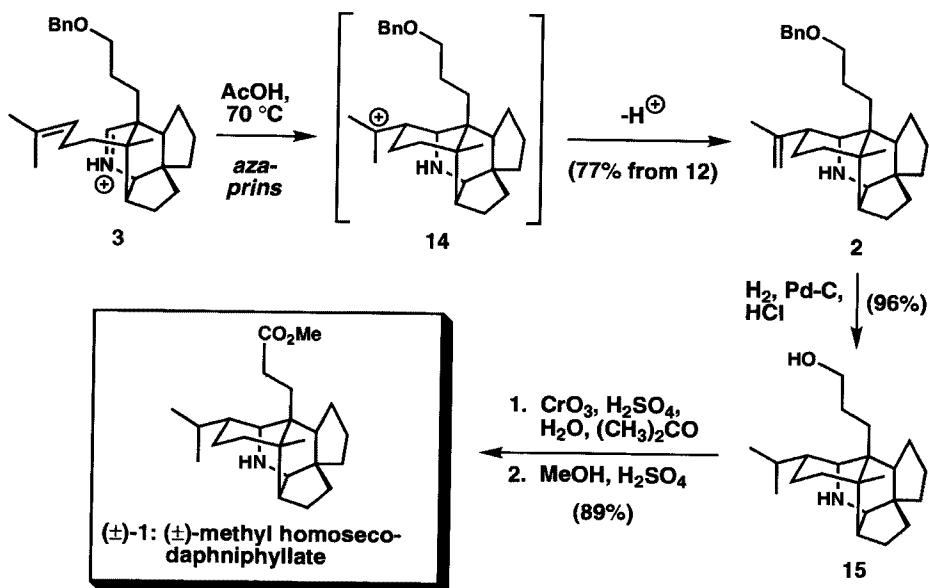
A complete reduction of the δ -lactone in **11** with lithium aluminum hydride affords an equimolar mixture of stereoisomeric diols **12** in an excellent yield of 96%. A Swern oxidation then completes the task of synthesizing intermediate **5**. Dialdehyde **5** is itself a rather labile intermediate; it was found to be susceptible to a retro-Michael fragmentation which opens the five-membered ring and destroys all three stereogenic centers in **5**. As a result, dialdehyde **5** is not isolated. It is treated directly with gaseous ammonia to give azadiene **13**, the unprotonated form of **4**. In this reaction, a molecule of ammonia most likely first attacks the less hindered of the two aldehyde carbonyls in **5**. After imine-enamine tautomerization, the nitrogen atom can then attack, in an intramolecular fashion, the neopentyl aldehyde, giving azadiene **13** after expulsion of a molecule of water. After concentration of the reaction mixture, the crude residue is dissolved in acetic acid at 25°C and then warmed to 70°C over a period of 1.5 h to give intermediate **2** in an overall yield of 77% from **12** (see Schemes 2 and 3). In this impressive polycyclization process, azadiene **13** is protonated by acetic acid to





Scheme 2. Synthesis of key intermediate **3**.

give **4** as a transient intermediate. At room temperature, this substance participates in a facile intramolecular Diels–Alder reaction⁵ to give intermediate **3**. Although intermediate **3** is a stable substance at 25 °C, it obligingly participates in an intramolecular cation π -type, or aza-Prins cyclization at 70 °C to afford pentacycle **2** through the intermediacy of tertiary cation **14** (Scheme 3). Thus, without isolating any intermediates, it is possible to achieve the conversion of diol **12** into a very close relative of methyl homosecodaphniphyllate in short order through a sequence of reactions employing inexpensive and readily available reagents. Along the path from diol **12** to intermediate **2**, it was found that azadiene **13** is, in the absence of acetic acid, a stable substance. However, in refluxing toluene **13** will participate in an intramolecular [4+2]



Scheme 3. Synthesis of (±)-methyl homosecodaphniphyllate [(±)-1].

cycloaddition reaction to give the unprotonated form of **3** with a half-life of about two hours. Remarkably, in the presence of acetic acid, the intramolecular Diels-Alder step is dramatically accelerated and is complete at 25 °C in less than five minutes!

With a secure route to pentacyclic amine **2**, the completion of the total synthesis of **1** requires only a few functional group manipulations. When a solution of **2** in ethanol is exposed to Pd-C in an atmosphere of hydrogen, the isopropenyl double bond is saturated. When a small quantity of HCl is added to this mixture, the hydrogenolysis of the benzyl ether is accelerated dramatically, giving alcohol **15** in a yield of 96%. Oxidation of the primary alcohol in **15** with an excess of Jones reagent, followed by Fischer esterification, gives (±)-methyl homosecodaphniphyllate [(±)-1] in an overall yield of 85% from **2**.

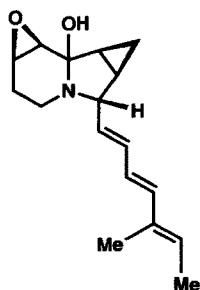
26.4 Conclusion

Tandem reaction strategies can accomplish several synthetic objectives in a single step.⁶ The rapidity with which they can build up molecular complexity is a most useful and impressive virtue. For example, cation-induced, biomimetic polyolefinic cyclizations⁷ are among the most productive and atom-economical⁸ single-step transformations known in organic chemistry. In one of the most spectac-

ular examples, a tetracyclic steroidal framework possessing seven stereogenic centers is assembled in one dramatic step from a flat polyolefin chain⁹ (see Chapter 6) in the absence of an enzyme! In the present synthesis, a tandem vicinal difunctionalization¹⁰ of α,β -unsaturated ester **7** introduces all of the carbon atoms that will constitute the complex pentacyclic framework of **1**. After a few conventional functional group manipulations, compound **5** is molded into an intermediate that can accommodate sequential intramolecular Diels–Alder and cation π -type reactions. It is noteworthy that this strategy accomplishes the total synthesis of (\pm)-methyl homosecodaphniphyllate [(\pm)-**1**] in nine steps and proceeds in 48 % overall yield from readily accessible starting materials. More than 3.5 g of racemic **1** have been prepared in short order by this elegant and powerful sequence.

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1: indolizomycin

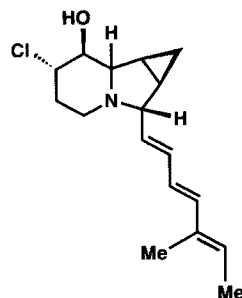
S. J. Danishefsky (1990)

Indolizomycin

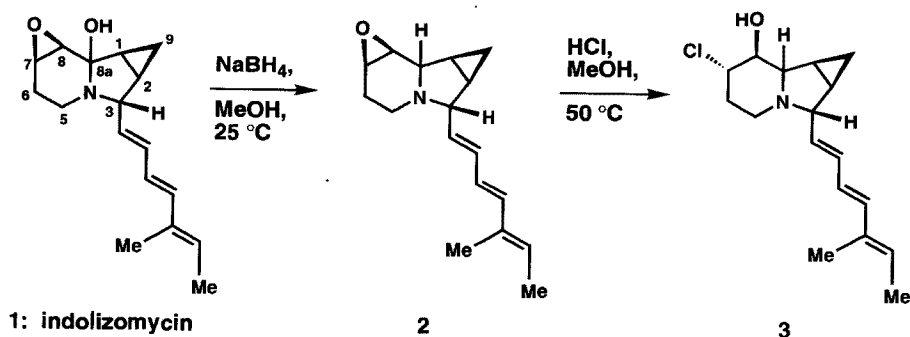
27.1 Introduction

In Japan, the interesting discovery was made that the union, by protoplast fusion, of two inactive *Streptomyces* strains, *Streptomyces tenjimariensis* NM16 and *Streptomyces grisline* NP1-1, afforded a particularly active clone (termed SK2-52) that produces the antibiotic indolizomycin (**1**).¹ Although this novel strategy for generating an antibiotic-producing clone from inactive parental strains does not reveal the genetic origin of **1**, it has stimulated some interesting proposals.² For example, it is tempting to entertain the hypothesis that the biosynthesis of indolizomycin features one or more enzymes that have arisen from recombinant genes. On the other hand, the daughter strain, SK2-52, may possess the appropriate mechanism(s) to express silent genes already present in one of the parents. The unusual structure of indolizomycin is likely due, in no small part, to its unconventional lineage.

It was on the basis of spectroscopic data and an X-ray crystallographic analysis of compound **3** (see Scheme 1) that the constitution of the indolizomycin molecule was revealed. Although the configuration at C-8a (see Scheme 1) remains unknown, these studies established the stereochemical relationships shown in **1**. The bicyclic indolizidine substructure of indolizomycin accommodates an array of interesting functional groups. Indeed, the oxiranyl and cyclopropyl rings, the hemiaminal linkage, and the conjugated triene moiety are all prominent structural features. As it turns out, by virtue of the particular arrangement of these groups, the indolizomycin molecule is very labile, decomposing rapidly at 25 °C under neutral conditions.



3

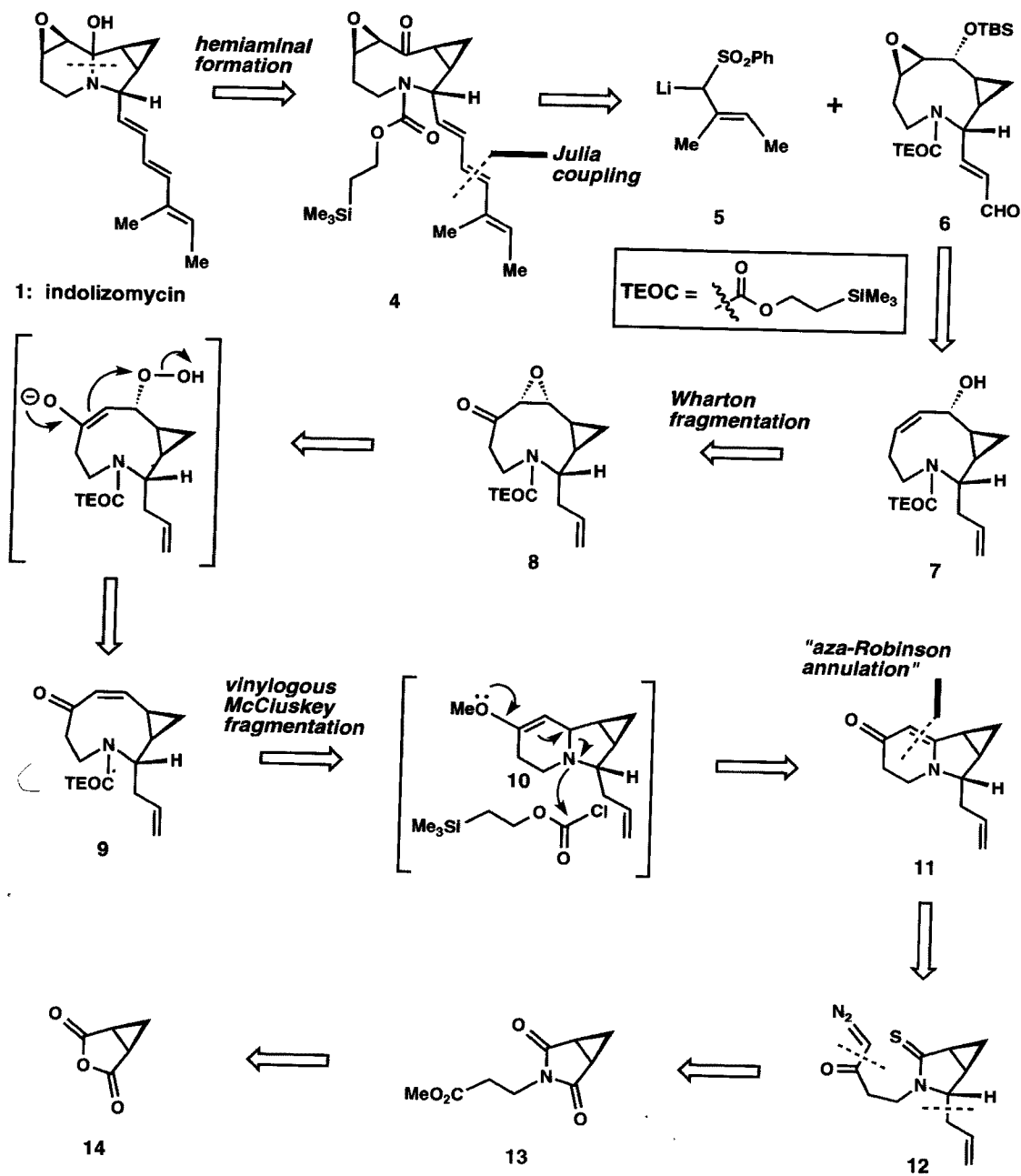


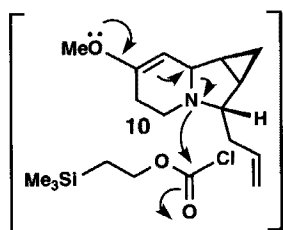
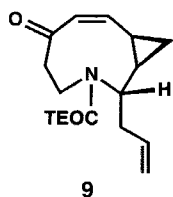
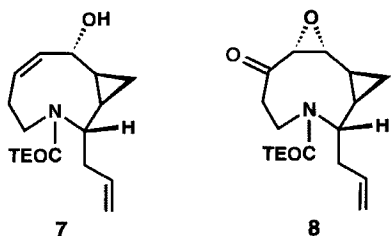
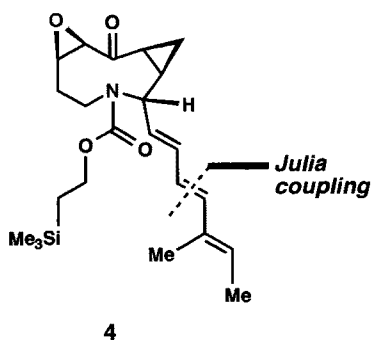
Scheme 1. Selected transformations of indolizomycin (**1**).

The fragility of this natural product notwithstanding, S.J. Danishefsky and his group at Yale disclosed, in 1990, the first chemical synthesis of racemic indolizomycin (**1**).² The construction of such a vulnerable substance in the laboratory is a most admirable achievement. The remainder of this chapter is devoted to Danishefsky's elegant total synthesis of (±)-indolizomycin [(±)-**1**].

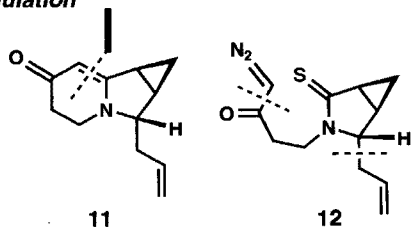
27.2 Retrosynthetic Analysis and Strategy

Although the unstable nature of indolizomycin was well documented at the outset, the pathway(s) by which it decomposes were never elucidated. Moreover, there was a lack of information regarding the compatibility of indolizomycin's functional groups with potential synthetic steps. It was known, however, that the action of sodium borohydride on **1** can bring about the reduction of the hemiaminal linkage to give compound **2** (see Scheme 1).^{1a} Interestingly, relative to indolizomycin, compound **2** is a more stable, more manageable substance, and it was surmised on this basis that the confluence of the hemiaminal linkage with the remaining functional groups renders indolizomycin susceptible to destructive processes. To achieve a total synthesis of indolizomycin, it would therefore be necessary to delay the introduction of the hemiaminal linkage to a late stage of the synthesis, preferably the very last stage. Key intermediate **4** (see Scheme 2) thus emerged as a potential precursor to indolizomycin. In the synthetic direction, it was anticipated that fluoride-induced deprotection of the azoninone nitrogen in **4** would be followed by a transannular carbonyl addition reaction to give **1**. This interesting maneuver is predicated on the assumption that the configuration of the C-8a stereocenter in the natural product is a

**Scheme 2.** Retrosynthetic analysis of indolizomycin (1).



"aza-Robinson
annulation"



consequence of thermodynamic control, and that the crucial transannular cyclization would deliver the more stable (natural) hemiaminal stereoisomer.

Although its role in the decomposition of indolizomycin has not been defined, the conjugated triene moiety probably contributes to the instability of the natural product. It was, therefore, decided to defer the introduction of this grouping to an advanced stage of the synthesis. The conjugated triene in **4** could, in principle, be fashioned in a variety of ways; nonetheless, the option afforded by retrosynthetic cleavage of the indicated bond in **4** appeared particularly attractive. It was anticipated that the convergent union of compounds **5** and **6** through a *trans*-selective Julia coupling³ would complete the construction of the labile triene side chain of the target compound (Scheme 2).

Through a short sequence of functional group manipulations, compound **6** could be elaborated from allylic alcohol **7**, the projected product of a Wharton fragmentation⁴ of epoxy ketone **8** (*vide infra*). In turn, compound **8** could be derived from enone **9**. In the synthetic direction, a Michael addition⁵ of hydroperoxide anion to enone **9** would be expected to take place from the less hindered side of the molecule. Epoxy ketone **8** would then form upon collapse of the intermediate enolate with concomitant expulsion of hydroxide ion (see arrows, Scheme 2).

A careful analysis of the constitution of compound **9** revealed the intriguing possibility of constructing its azonine ring system through fragmentation of an indolizidine such as intermediate **11**. In the synthetic direction, alkylation of the Lewis-basic vinylogous amide oxygen in **11** with Meerwein's salt (Me_3OBF_4), followed immediately by metal hydride reduction of the resulting iminium ion could furnish **10**. The hope was that **10** could serve as a viable substrate for an interesting vinylogous McCluskey fragmentation.⁶ In principle, the action of a chloroformate on **10** could bring about the transformations illustrated (see arrows, Scheme 2) to give compound **9**; although a concerted sequence is shown, it is presumed that a transient ammonium ion resulting from the acylation of the nitrogen atom in **10** would initiate the desired ring fragmentation.

By contrast to azoninone **9**, tricyclic indolizidine **11** was considered to be a more readily accessible synthetic intermediate. In fact, the anticipated facility with which compound **11** could be assembled was an important factor that guided the adoption of the novel vinylogous McCluskey fragmentation strategy for the construction of azoninone **9**. Retrosynthetic disassembly of vinylogous amide **11** in the manner illustrated in Scheme 2 reveals diazo ketone **12** as a potential precursor. The projected conversion of compound **12** to **11** is equivalent to an aza-Robinson annulation and is related to the Eschenmoser sulfide contraction.⁷ Diazo ketone **12** could be derived in a few steps from substituted imide **13**, and the latter substance could in turn be fashioned from the well-known anhydride **14**.⁸ The selection of compound **14** as the starting compound is very logical, for it possesses the cyclopropane

function that will eventually reside in the natural product. The application of this basic plan to the first total synthesis of (\pm)-indolizomycin [(\pm)-**1**] is presented in Schemes 3-7.

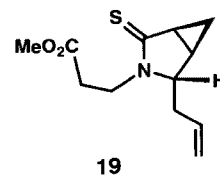
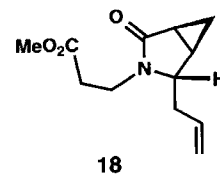
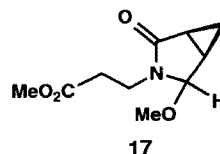
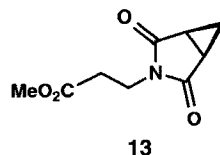
27.3 Total Synthesis

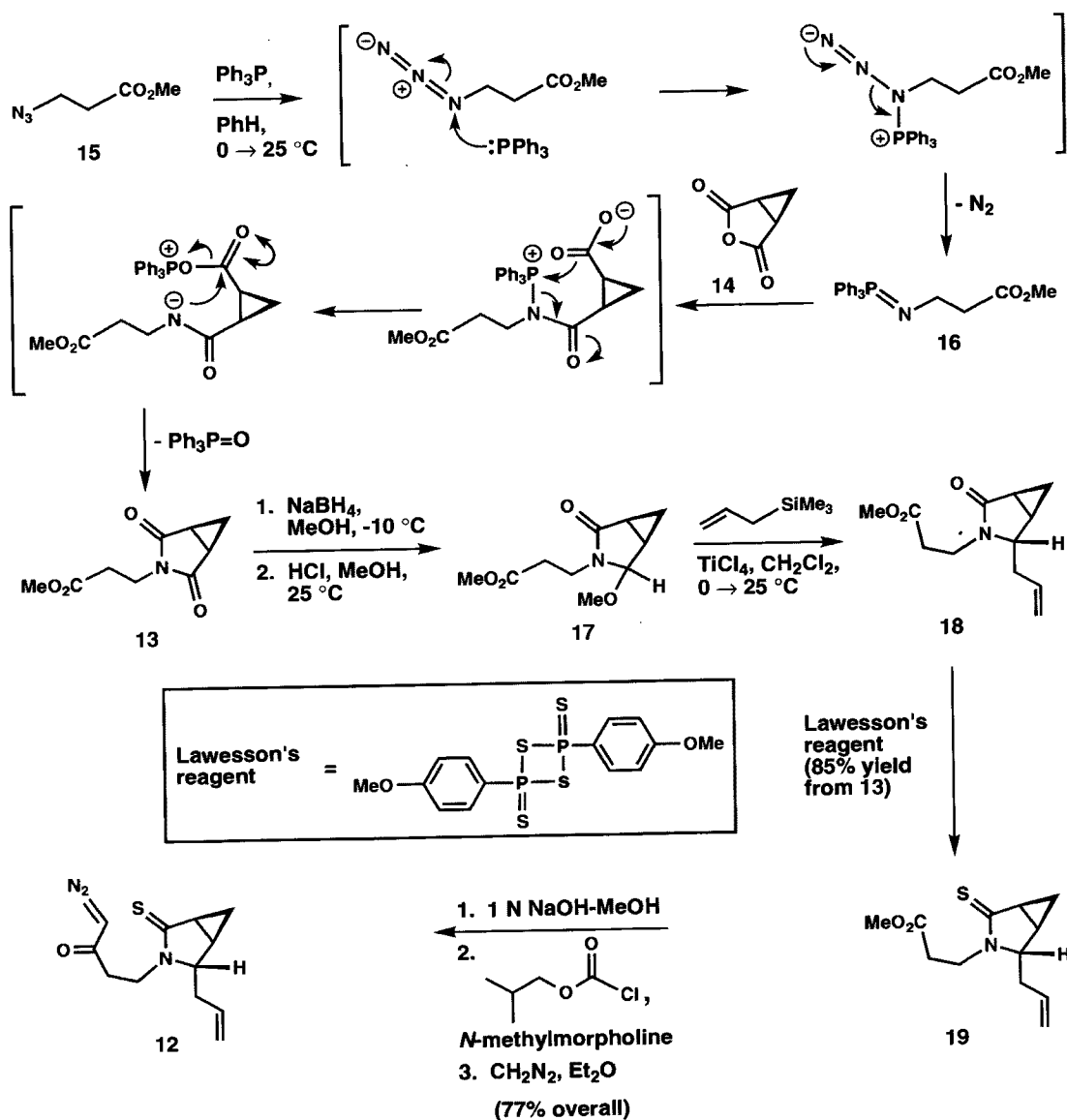
Danishefsky's synthesis of indolizomycin commences with the conversion of anhydride **14** to imide **13** (see Scheme 3).⁹ This interesting transformation includes the reaction of triphenylphosphine with methyl 3-azidopropionate (**15**) to give *N*-(triphenylphosphoranylidene)- β -alanine methyl ester (**16**). The latter substance then reacts efficiently with anhydride **14** to give imide **13**. Exposure of **13** to the action of sodium borohydride results in a chemoselective reduction of one of the imide carbonyls and furnishes a hydroxy amide which subsequently undergoes conversion to **17** in the presence of acidic methanol. On treatment with titanium tetrachloride and allyltrimethylsilane, methoxy aminal **17** is transformed into an electrophilic *N*-acyliminium ion which is immediately captured in an intermolecular reaction with allyltrimethylsilane to give allyl lactam **18**;¹⁰ with the β face of the *N*-acyliminium ion blocked by the cyclopropane ring, the allylation reaction takes place from the less hindered α face and furnishes **18** as a single diastereoisomer. It should be noted that the C-3 allyl substituent is a convenient and stable precursor for the labile triene side chain of the natural product.

Although neither of the two carbonyl groups in **18** is immune to the action of Lawesson's reagent,¹¹ it is possible to bring about the selective conversion of the more Lewis-basic lactam carbonyl to the corresponding thiocarbonyl. Thus, treatment of **18** with Lawesson's reagent results in the formation of thiolactam **19** in 85% overall yield from **13**.

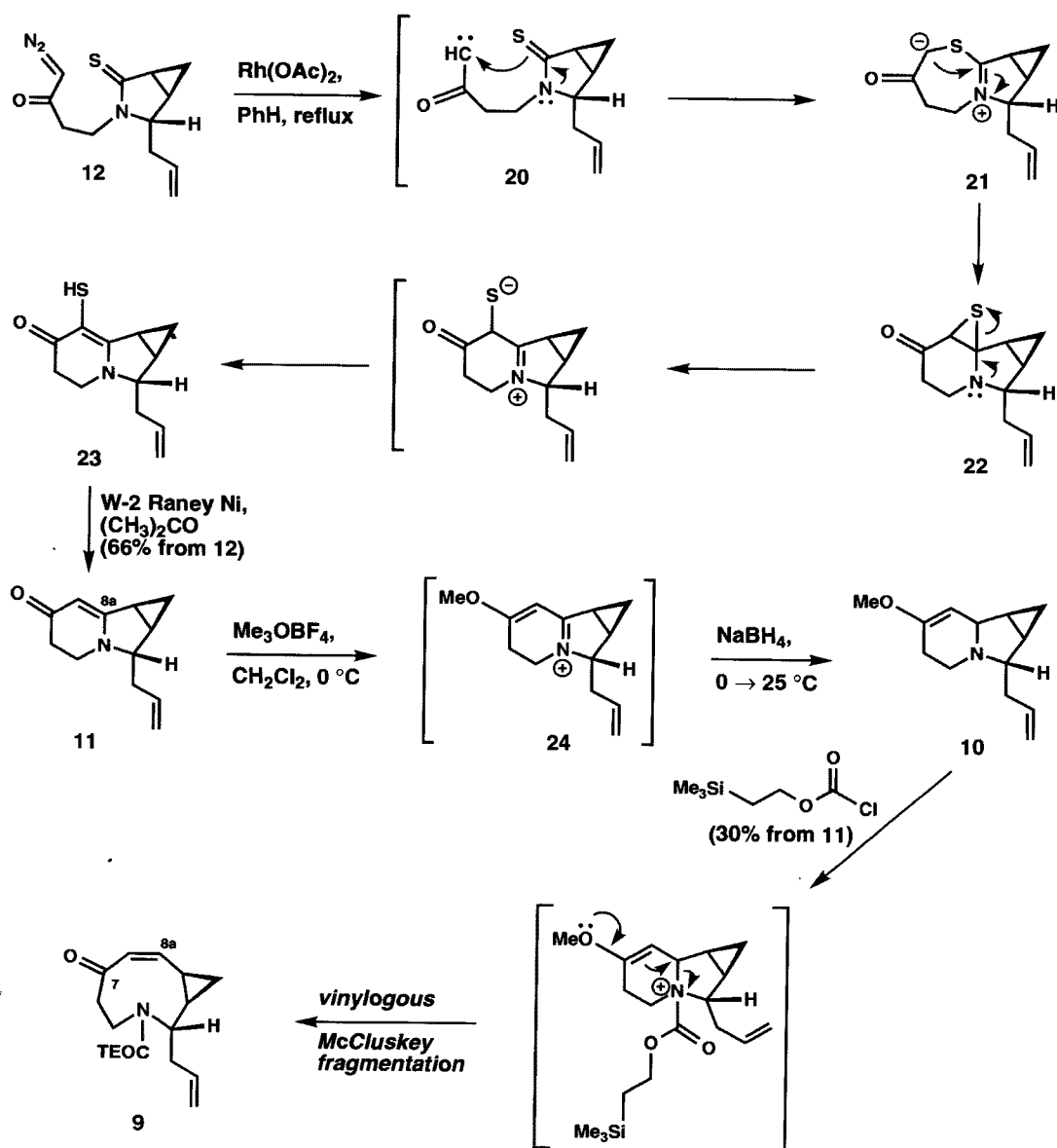
To set the stage for the crucial aza-Robinson annulation, a reaction in which the nucleophilic character of the newly introduced thiolactam function is expected to play an important role, it is necessary to manipulate the methyl propionate side chain in **19**. To this end, alkaline hydrolysis of the methyl ester in **19**, followed by treatment of the resulting carboxylic acid with isobutyl chloroformate, provides a mixed anhydride. The latter substance is a reactive acylating agent that combines smoothly with diazomethane to give diazo ketone **12** (77% overall yield from **19**).

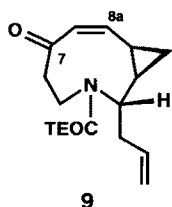
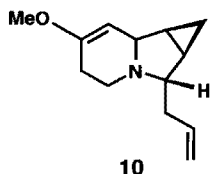
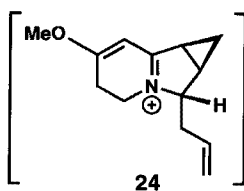
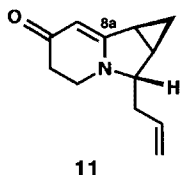
In the context of **12**, the diazo keto function and the thiolactam are in proximity. This circumstance would seem to favor any process leading to the union of these two groupings. It is conceivable that decomposition of the diazo function in **12** with rhodium(II) acetate would furnish a transitory electron-deficient carbene which would be rapidly intercepted by the proximal thiolactam sulfur atom (see **20**, Scheme 4). After spontaneous ring contraction of the





Scheme 3. Synthesis of intermediate 12.

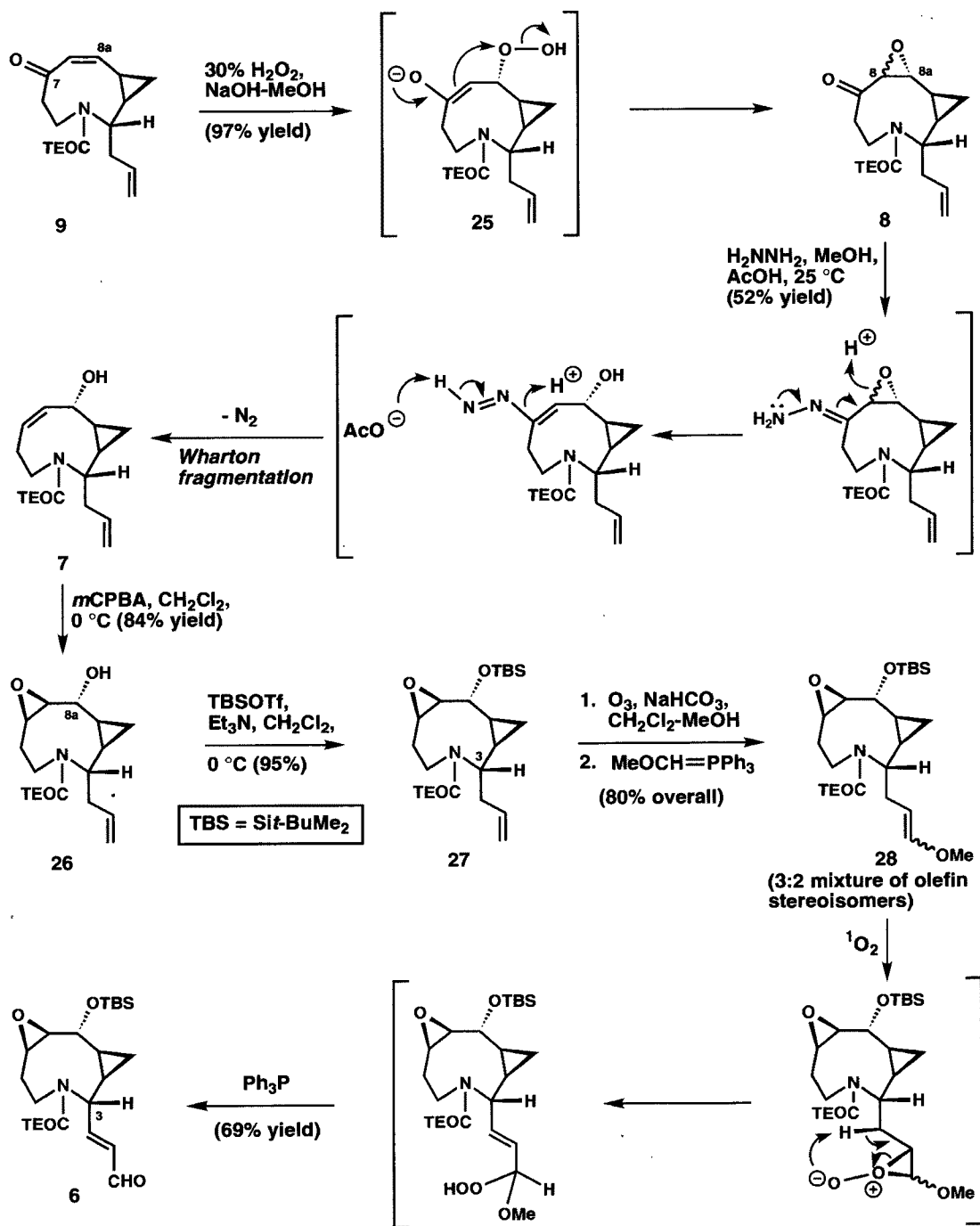
**Scheme 4.** Synthesis of intermediate 9.



newly formed sulfur-bridged intermediate **21**, the putative episulfide (thiirane) **22** could then isomerize to vinylogous amide **23**. This productive and novel transformation is synthetically equivalent to an aza-Robinson annulation,¹² and is analogous to the alkylative version of the Eschenmoser sulfide contraction.⁷ Although the identity of the sulfur-containing compound **23** was not confirmed, treatment with W-2 Raney nickel afforded a new compound which was shown to be the desired vinylogous amide **11**. The yield of **11** from **12** is 66%.

The relationship between indolizidine **11** and the targeted azoninone **9** is actually very close; the conversion of the former substance to the latter can be accomplished in the event that the N-C8a bond can be cleaved. It will be noted that the carbonyl oxygen atom in **11** is part of a vinylogous amide system and is, therefore, reasonably nucleophilic. Thus, it is not surprising that the action of trimethyloxonium tetrafluoroborate (Meerwein's salt)¹³ on **11** can effect a smooth methylation of the vinylogous amide carbonyl oxygen to give **24**. The latter substance is not isolated; the iminium function in **24** is reduced with sodium borohydride to give enol ether **10**. Gratifyingly, treatment of a solution of **10** in benzene with 2-(trimethylsilyl)ethyl chloroformate at 25°C accomplishes the desired vinylogous McCluskey fragmentation and furnishes azoninone **9** in 30% yield from **11**. Although the yield for this three-step sequence is modest, the azoninone product contains a valuable enone function which could be used in the elaboration of the requisite C7-C8a functionality.

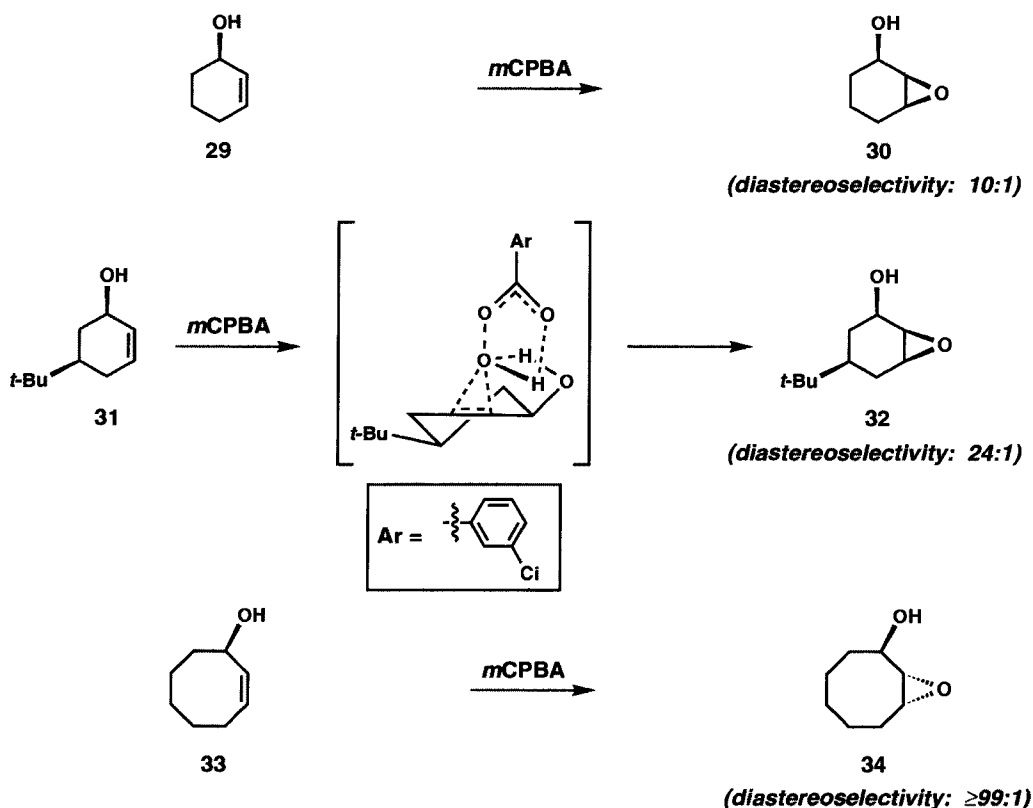
Enone **9** is an ambident electrophile; it possesses electrophilic potential at C-7 and at C-8a (see Scheme 5). One of the more obvious reactions in which enone **9** can participate is a conjugate or Michael addition reaction.⁵ Indeed, in the presence of alkaline hydrogen peroxide, the electrophilic β -carbon atom of **9** suffers a nucleophilic attack by hydroperoxide anion from the less hindered side of the molecule, giving rise to enolate **25**. Although this Michael addition reaction is reversible, enolate **25** can participate in an irreversible, intramolecular etherification reaction (see arrows) to give α,β -epoxy ketone **8**. This reaction actually affords a mixture of epoxy ketone diastereoisomers epimeric at C-8 (97% yield). Internal bond rotation followed by trapping of the enolate could account for the production of C-8 epoxy ketone epimers. It is noteworthy that the formation of diastereomeric substances at this stage in the synthesis does not present a problem because the pending Wharton epoxy ketone fragmentation will destroy the very stereocenter that could not be defined in the previous step. Indeed, exposure of the mixture of epimeric epoxy ketones to the action of hydrazine in MeOH-AcOH at 25°C furnishes a transient epoxy hydrazone which subsequently participates in a Wharton fragmentation⁴ (see arrows) to give allylic alcohol **7** in stereoisomerically pure form. Although an ionic mechanism for the decomposition of the intermediate epoxy hydrazone is shown in Scheme 5, the formation of a vinyl radical which subsequently reacts with hydrogen



Scheme 5. Synthesis of intermediate 6.

radical may be operative.¹⁴ You will note that this outcome would not have been possible had the precursor epoxy ketones differed in configuration at C-8a.

A digression is in order at this stage. From the pioneering work of Henbest and Wilson,¹⁵ it is known that cyclic allylic alcohols such as **29** and **31** (see Scheme 6) can be diastereoselectively epoxidized with peroxybenzoic acid or *meta*-chloroperoxybenzoic acid (*m*CPBA) to give the corresponding *cis*-epoxy alcohol diastereomers, compounds **30** and **32**, respectively. In these peracid oxidations, it is currently believed that a pseudo-equatorial hydroxyl group directs the stereochemical course of the epoxidation event (see **31** → **32**, Scheme 6).¹⁶ Interestingly, exposure of medium-ring allylic alcohol **33** to the same oxidant results in the stereoselective formation of *trans*-epoxy alcohol **34**.¹⁷ The preferred transition state conformation for the epoxidation of 2-cycloocten-1-ol (**33**) with *m*CPBA is characterized by an equatorially oriented hydrogen-bonded complex. In this arrangement, which is favored on



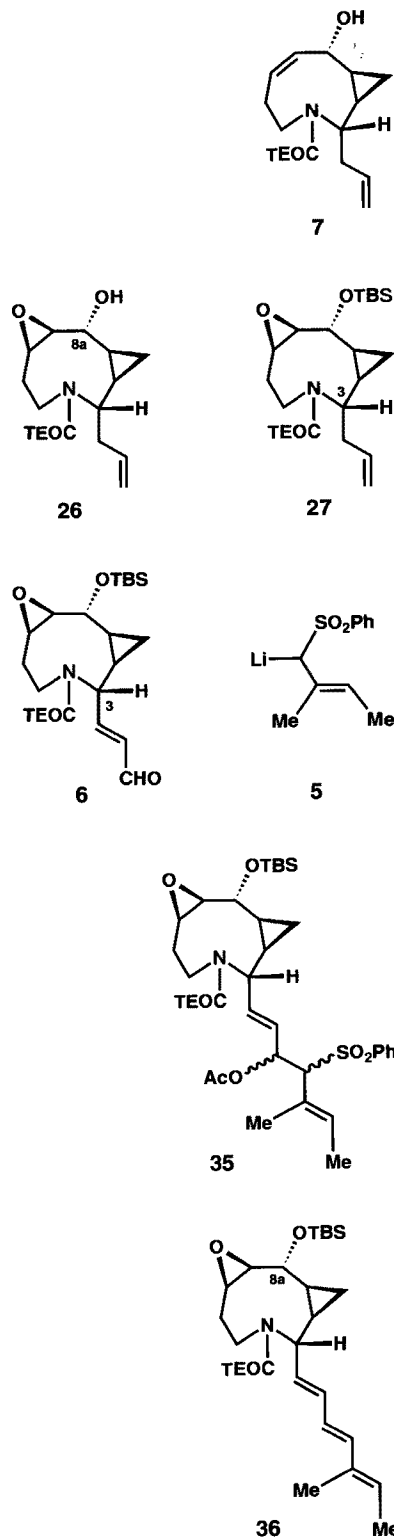
Scheme 6. Hydroxyl-directed epoxidations.

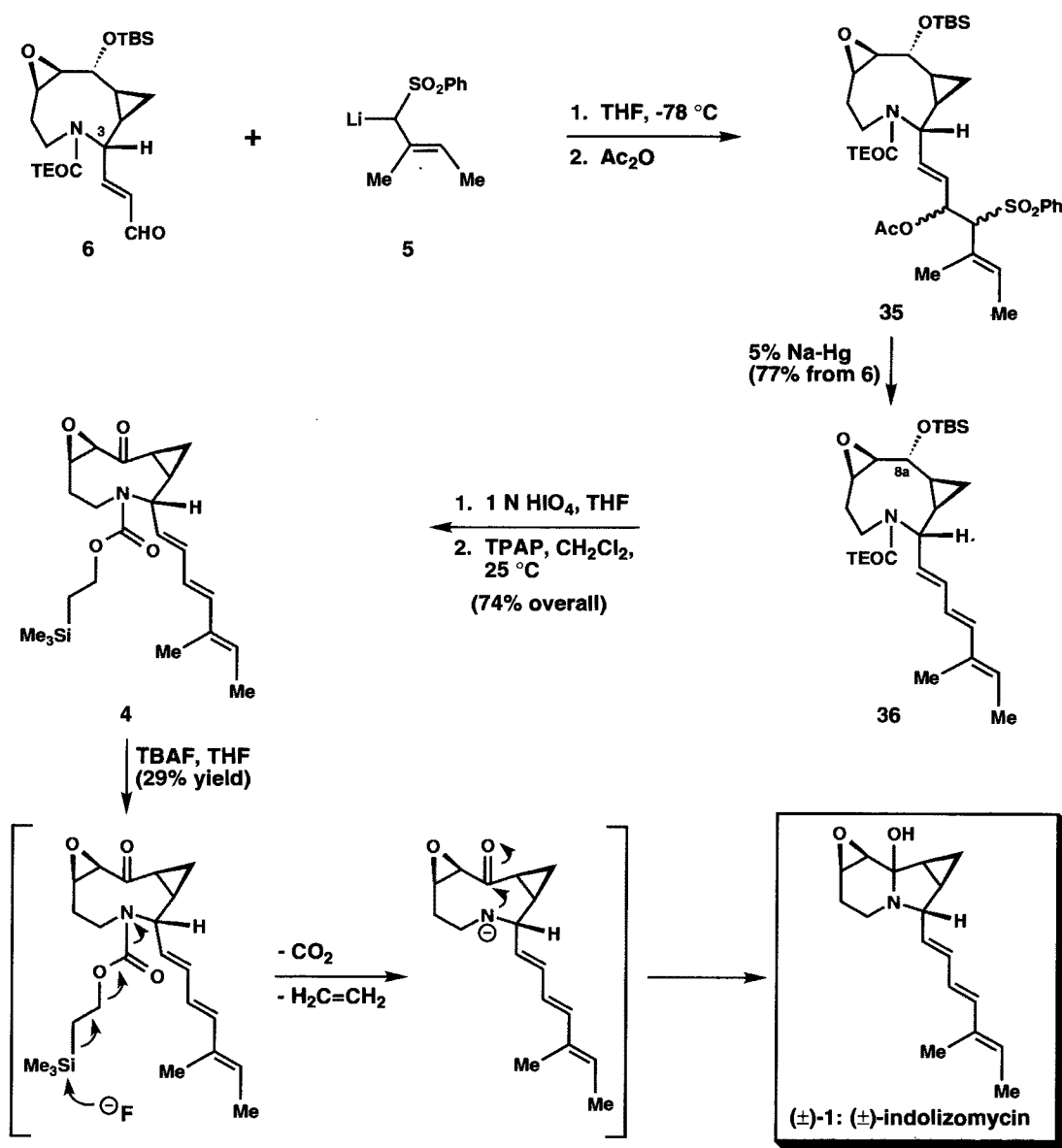
steric grounds, the hydroxyl group directs the oxidation of the much less hindered peripheral alkene diastereoface, giving *trans*-epoxy alcohol **34** with exceptional stereoselectivity ($\geq 99:1$). On the basis of this precedent, it was anticipated that the action of *m*CPBA on medium-ring allylic alcohol **7** (see Scheme 5) would accomplish the formation of the corresponding *trans*-epoxy alcohol stereoisomer. Gratifyingly, treatment of a solution of **7** in CH_2Cl_2 with *m*CPBA at 0°C provides the desired *trans*-epoxy alcohol **26** in 84 % yield; the stereoisomeric *cis*-epoxy alcohol is not observed in this reaction. Protection of the free C-8a secondary hydroxyl as a *tert*-butyldimethylsilyl (TBS) ether then furnishes compound **27** in 41 % overall yield from **8**.

We have reached a critical stage in the synthesis. We have retraced the elegant reaction sequences that have allowed the construction of much of indolizomycin's functionality, and we are now in a position to address the introduction of the sensitive triene side chain. A prerequisite for an evaluation of the Julia coupling strategy described previously in Scheme 2 is the conversion of the C-3 allyl side chain in **27** to the α,β -unsaturated aldehyde side chain found in **6**. To this end, oxidative cleavage of the carbon-carbon double bond in **27** with ozone furnishes an aldehyde that reacts smoothly with (methoxymethylene)triphenylphosphorane to give the one-carbon homologated enol ether **28** (80 % overall yield). It is of no consequence that this Wittig reaction provides a 3:2 mixture of stereoisomeric enol ethers because both substances react with singlet oxygen^{18,19} and undergo conversion to the same enal **6** (69 % yield) after reduction of the intermediate hydroperoxides with triphenylphosphine (see Scheme 5). This transformation is often referred to as the Conia photooxygenation.

Although the C-3 stereocenter in **6** may be susceptible to epimerization in the presence of a basic organolithium reagent, enal **6** condenses smoothly in the desired and expected way with lithio sulfone **5** at -78°C to give, after quenching with acetic anhydride, a stereoisomeric mixture of acetoxy sulfones (see **35**, Scheme 7). (*E,E,E*)-Triene **36** is then unveiled on reduction of the stereoisomeric acetoxy sulfones with 5 % sodium amalgam (77 % overall yield from **6**).³

With the C-3 triene side chain and the two three-membered rings positioned correctly in space, there remain only a few obstacles on the path to indolizomycin. The goal at this advanced stage of the synthesis was to create a C-8a ketone; indolizomycin could then, in principle, be revealed on deprotection of the azoninone nitrogen atom. During the course of their work, the Danishefsky group found that the simultaneous liberation of the C-8a secondary hydroxyl and the amino group produced an amino alcohol that could not be converted to the natural product by oxidation. It would therefore be necessary to bring about a selective cleavage of the C-8a TBS ether so that the crucial oxidation could be performed on a substance in which the amine functionality was still protected. Although it is customary to cleave silyl ethers with fluoride ion,²⁰





Scheme 7. Synthesis of (±)-indolizomycin [(±)-1].

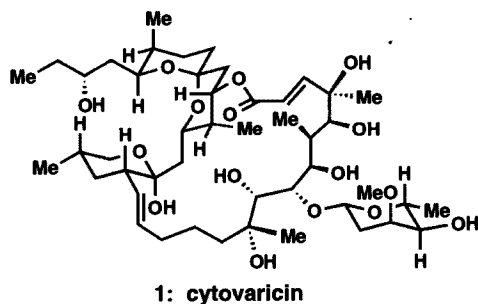
it is very likely that the trimethylsilylethoxycarbonyl (TEOC) protecting group attached to the nitrogen atom would also be cleaved in the presence of fluoride ion. After a good deal of experimentation, it was fortuitously discovered that the action of 1 *N* aqueous periodic acid in THF on compound **36** can accomplish the completely selective cleavage of the C-8a TBS ether. Oxidation of the resulting alcohol with tetra-*n*-propylammonium perruthenate (TPAP)²¹ then provides the penultimate intermediate, ketone **4**, in 74% overall yield from **36**. The supposition that the TEOC carbamate would be cleaved in the presence of fluoride ion was in fact validated when it was found that treatment of **4** with tetra-*n*-butylammonium fluoride (TBAF) resulted in the formation of (±)-indolizomycin [(±)-**1**]. As expected, the unveiling of the azoninone nitrogen is attended by a facile transannular carbonyl addition reaction to give the natural product. The total synthesis of the sensitive indolizomycin molecule is now complete.

27.4 Conclusion

Danishefsky's creative and instructive synthesis of indolizomycin features a number of very interesting transformations. The intramolecular interception of an electron-deficient carbene by a nucleophilic thioamide and concomitant sulfide contraction constitutes an effective aza-Robinson annulation method.¹² This method, the synthetic equivalent of the cyclodehydration of a keto amide, played a key role in a short and efficient synthesis of tricyclic dihydropyridone **11**. Although indolizomycin (**1**), like intermediate **11**, possesses a bicyclic indolizidine frame, it was shown that a nine-membered azoninone skeleton can provide a very favorable setting for the introduction of the remaining functional groups. In a most impressive transformation, a vinylogous McCluskey fragmentation of an indolizidine (see **10** → **9**, Scheme 4) provided a convenient entry into the azoninone series. The Wharton fragmentation of an epoxy ketone (see **8** → **7**, Scheme 5), and the application of the Conia photooxygenation process are also noteworthy maneuvers in this synthesis. The Danishefsky synthesis of the labile, bioengineered alkaloid indolizomycin is a masterful achievement of contemporary organic synthesis.

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D. A. Evans (1990)

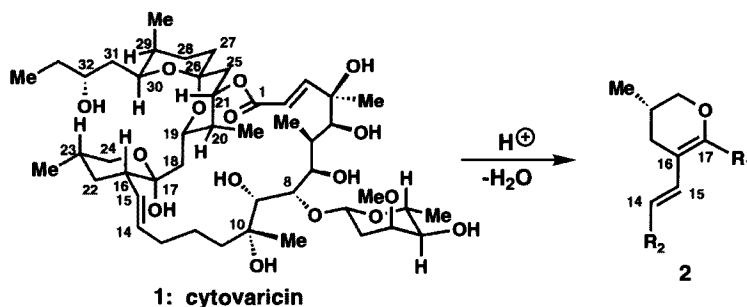
Cytovaricin

28.1 Introduction

Acyclic stereochemical control has traditionally been achieved through the assembly of a cyclic template and the use of a preexisting center(s) of asymmetry to guide the introduction of new asymmetry. Through relative asymmetric induction, a stereochemically defined cyclic framework is formed and then opened to reveal a stereodefined acyclic molecule. The impressive achievements of the Corey,¹ Woodward,² and Stork³ groups in the erythromycin field exemplify the merits of this strategy.⁴ Nevertheless, the early 1980's witnessed the emergence of a new strategy for the achievement of acyclic stereochemical control. Central to this new approach is the use of enantiomerically pure reagents and auxiliaries for the purpose of elaborating stereochemically complex acyclic molecules. Drawing inspiration from the complex structures of the macrolide and ionophore antibiotics, several groups focused on the development of stereoselective variants of the aldol condensation. The pioneering efforts of Evans,⁵ Masamune,⁶ Heathcock,⁷ and Mukaiyama⁸ have deepened our understanding of the factors which govern aldol stereoselection and have extended the utility of the aldol condensation as a tool in natural product synthesis. The work of D. A. Evans and his group, in particular, has had a profound impact on organic synthesis. The asymmetric aldol and enolate alkylation methodologies developed by Evans rank among the most reliable stereoselective bond construction methods and have performed admirably in total syntheses of some exceedingly complex natural products.⁹ This chapter features the convergent, asymmetric total synthesis of the antineoplastic macrolide antibiotic cytovaricin (**1**) by D. A. Evans and his group at Harvard.¹⁰

In 1981, Isono and coworkers reported the isolation and antineoplastic activity of cytovaricin.¹¹ The spiroketal macrolide cytovaricin produced by *Streptomyces diastatochromogenes*, displays significant inhibitory activity against Yoshida sarcoma cells *in vitro*. Two years after their initial report, Isono *et al.* disclosed the results of an X-ray crystallographic analysis which confirmed the constitution and relative stereochemistry of cytovaricin.¹² It was also demonstrated that the previously known glycoside, methyl- β -D-cymaroside, is produced by degradation of cytovaricin (**1**) with methanol and acid, thereby securing the absolute configuration of the macrolide.¹³

The cytovaricin molecule is extremely complex. Its highly oxygenated 22-membered lactone ring is the host of a contiguous array of seven stereogenic centers, one of which is distinguished by a β -linked cymarosyl sugar moiety (see position 8). Perhaps its most salient structural feature is its 1,7-dioxaspiro[5.5]undecane framework. Cytovaricin is one of many spiroketal containing natural products which benefit from maximum anomeric stabilization due to a bisaxial arrangement of the two spiro carbon-oxygen bonds.¹⁴ The lactol moiety (position 17) is also an interesting structural feature. Cytovaricin crystallizes in its lactol form. Although the macrolide possesses the potential for ring-chain tautomerism, NMR studies in a number of solvents reveal that cytovaricin exhibits a large equilibrium preference for the closed lactol form. During the course of studies which were carried out to assess the stability of cytovaricin under a variety of reaction conditions, it was discovered that the lactol portion of the natural product undergoes facile and irreversible dehydration to UV-active dienol ether **2** under mildly acidic conditions (see Scheme 1). It is likely that the



Scheme 1. Acid-catalyzed dehydration of cytovaricin (**1**).

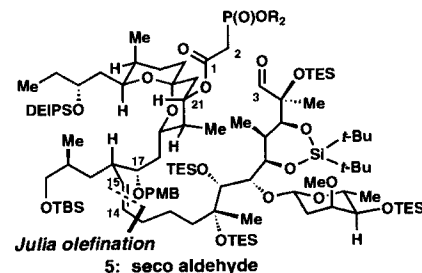
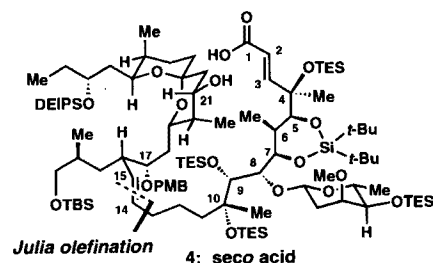
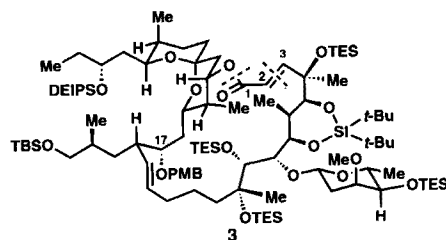
site of unsaturation between carbons 14 and 15 provides the seed for the destruction of the lactol structure by labilizing the adjacent C16-H bond. Lactol dehydration at any stage in the synthesis would constitute a serious setback because all efforts to rehydrate the dienol ether were uniformly unsuccessful.

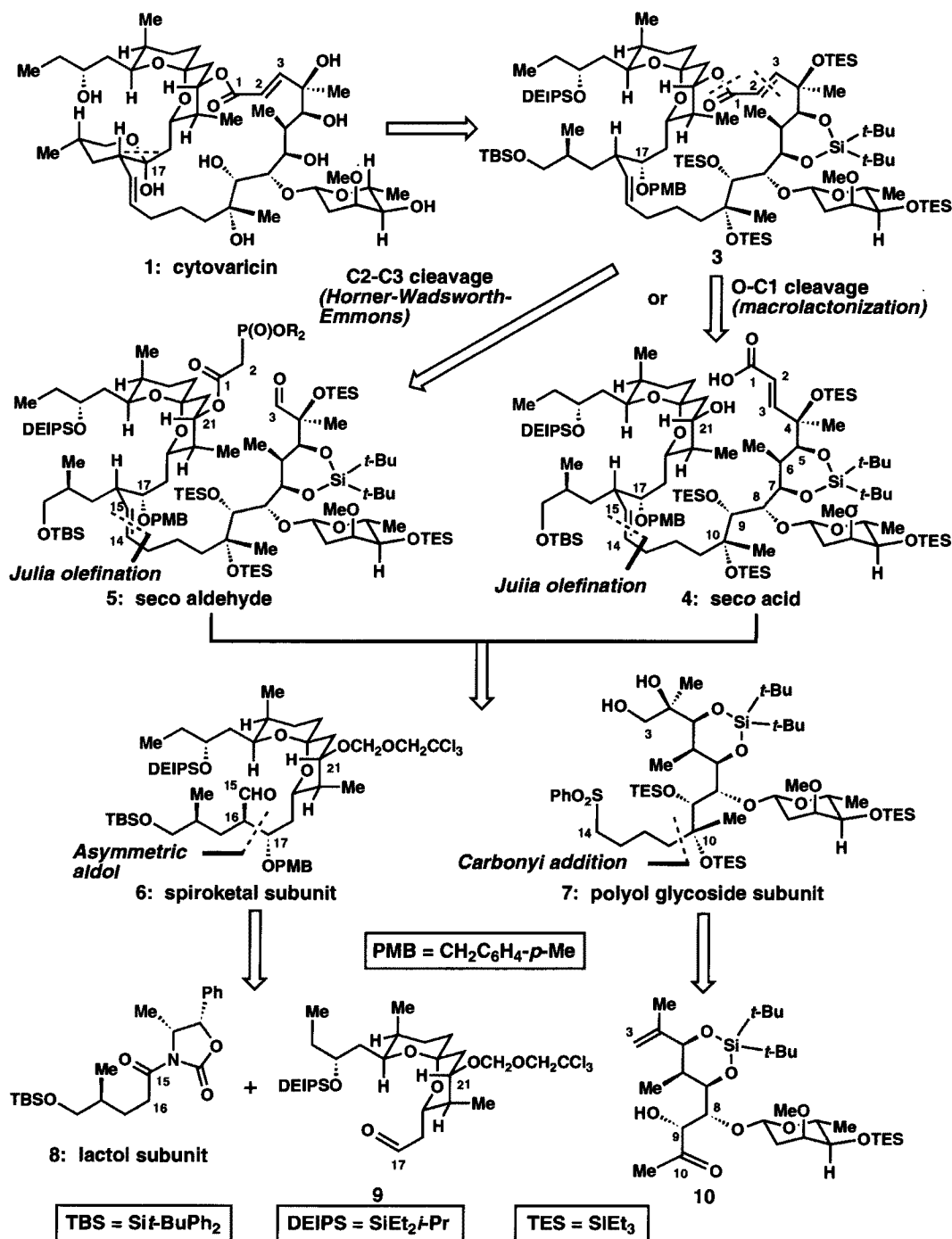
When addressing polyhydroxylated natural products as targets for total synthesis, it is common to employ silicon protecting groups. Silyl ethers are formed easily, are tolerant to a wide range of reaction conditions, and are usually removed easily with fluoride ion.¹⁵ Thus, it was gratifying to discover that the lactol functionality in cytovaricin is sufficiently stable to pyridinium hydrofluoride, provided that the medium is buffered with excess pyridine. Exposure of the natural product to tetra-*n*-butylammonium fluoride in THF resulted in rapid decomposition. On the basis of the pronounced acid lability of the lactol functionality in cytovaricin, it was decided to defer lactol formation to a very late stage in the synthesis and to employ silicon protecting groups which can be removed at room temperature with buffered pyridinium hydrofluoride.

28.2 Retrosynthetic Analysis and Strategy

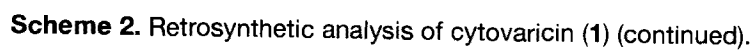
The cytovaricin lactol is simply an internal hemiketal; it forms uneventfully from an intramolecular attack on a C-17 ketone carbonyl by a C-24 primary hydroxyl group. As we have seen, this lactol must be handled very carefully, for it exhibits a propensity to dehydrate even under mildly acidic conditions. It is, therefore, necessary to postpone its introduction to the final step of the synthesis. Retrosynthetic disassembly of the sensitive lactol of cytovaricin (**1**) furnishes the reduced and protected intermediate **3** as a potential precursor (see Scheme 2). In the synthetic direction, selective deprotection and oxidation of the C-17 secondary hydroxyl group to the corresponding ketone, followed by a final deprotection step, would complete the synthesis of cytovaricin. At the outset, it was recognized that cytovaricin presents several viable options for macrocyclization.¹⁶ Seco acid **4** is derived from retrosynthetic scission of the O-C1 bond, and could conceivably be induced to undergo, in the synthetic direction, a macrolactonization reaction. Alternatively, retrosynthetic cleavage of the C2-C3 double bond affords seco aldehyde **5** and introduces the interesting possibility of achieving macrocyclization through an intramolecular Horner-Wadsworth-Emmons reaction. It is interesting to note that intermediates **4** and **5** could originate from common precursors. Retrosynthetic disassembly of **4** and **5** in the indicated way furnishes two intermediates of comparable complexity. Intermediates **6** and **7** represent the left- and right-hand sectors of cytovaricin, respectively, and it was projected that the C14-C15 double bond could be constructed during the course of a convergent union of these two intermediates through a *trans*-selective Julia olefination sequence.¹⁷

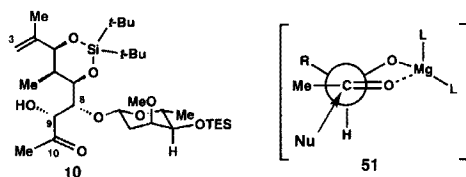
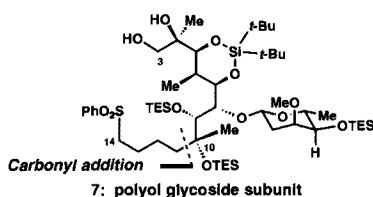
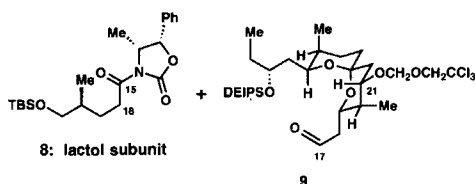
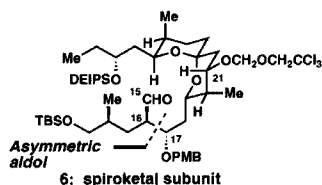
The synthetic problem is now reduced to the enantioselective construction of the two sectors of cytovaricin, intermediates **6** and **7**, and it was anticipated that this objective could be achieved through the application of asymmetric aldol, alkylation, and epoxi-





Scheme 2. Retrosynthetic analysis of cytoovaricin (1).





dation methodology. It is interesting to note that with the exception of the glycoside, all of the chirality in the natural product is ultimately obtained from the (1*S*,2*R*)-norephedrine-derived oxazolidone auxiliary. Disassembly of the spiroketal subunit **6** by cleavage of the indicated bond furnishes oxazolidone **8** and spiroketal aldehyde **9** as potential precursors. In the synthetic direction, a stereocontrolled aldol condensation between a (*Z*)-boron enolate derived from **8** and aldehyde **9** could achieve the formation of the C16-C17 bond. A few straightforward functional group modifications would then complete the assembly of **6**. The stereochemically complex linear molecule, intermediate **13**, is derived from retrosynthetic simplification of spiroketal **9**. Compound **13** is a vinylogous amide which could be assembled in a single step through acylation of the metalloenamine derived from hydrazone **14** with Weinreb amide **15**; compound **13** possesses electrophilic potential at C-26 and, under suitably acidic conditions, could participate in a spiroketalization reaction. Of course, acid catalyzed hydrolysis of both the acetonide and C-19 triethylsilyl ether protecting groups are prerequisites for this process. Methyl ketone **16**, the retrosynthetic precursor of dimethylhydrazone **14**, can be simplified in a very straightforward manner as shown in Scheme 2. It was projected that a *syn* aldol bond construction using chiral imide enolate methodology (**20**+**21**) could secure the formation of the stereogenic centers at carbons 29 and 30. The relative and absolute stereochemical relationships in intermediate **15** could also be secured through the use of Evans's asymmetric aldol methodology (**21**+**22**).

Asymmetric aldol methodology was also expected to play a key role in the synthesis of the polyol glycoside subunit, intermediate **7**, which can be traced to compound **10** (Scheme 2). Retrosynthetic cleavage of both the glycosidic and C8-C9 bonds in **10** affords the glycolate derived imide **11** and aldehyde **12** as potential precursors. In the synthetic direction and on the basis of precedent established in Evans's laboratory,^{9a} it was anticipated that a *syn* aldol bond construction between the chiral glycolate enolate derived from **11** and aldehyde **12** would create the two stereogenic centers at carbons 8 and 9 in the desired sense. Glycosidation of the free C-8 hydroxyl group and a few functional group manipulations would then afford **10**. The absolute configuration of the hydroxyl-bearing stereocenter at C-9 is such that it could be possible to define the stereocenter at C-10 in **7** through an α -chelation controlled¹⁸ addition of 4-(phenylthio)-*n*-butylmagnesium bromide to the ketone carbonyl in **10** (see **51**, Scheme 10). After protection of the vicinal hydroxyl groups as triethylsilyl ethers, simultaneous oxidation of the geminally disubstituted olefin and the phenylthio group would then complete the synthesis of **7**.

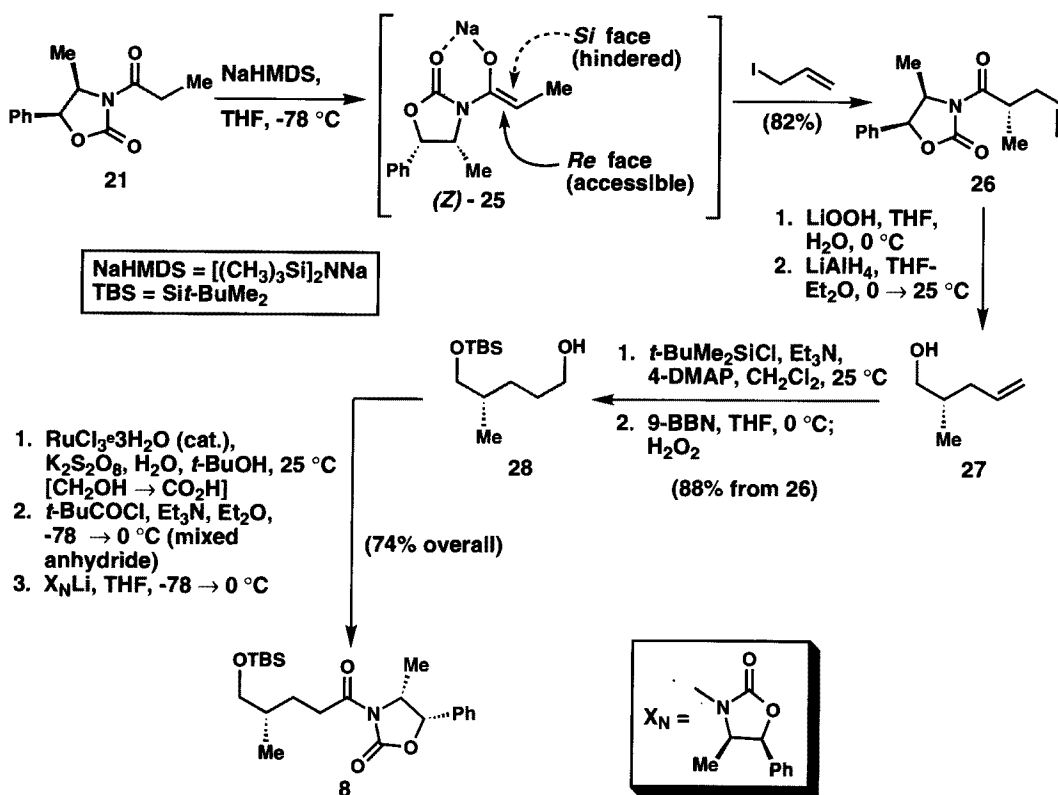
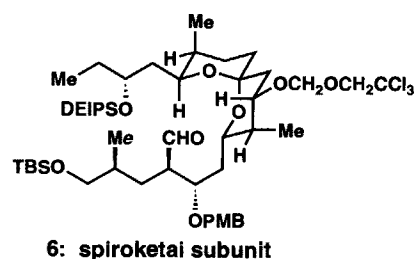
It was anticipated that two of the three stereochemical relationships required for intermediate **12** could be created through reaction of the boron enolate derived from imide **21** with α -(benzyloxy)acetaldehyde **24**. After conversion of the *syn* aldol adduct into enone **23**, a substrate-stereocontrolled 1,2-reduction of the C-5 ketone car-

bonyl would then accomplish the introduction of the third and final stereogenic center in **12**. The execution of this elegant and convergent strategy is described below.

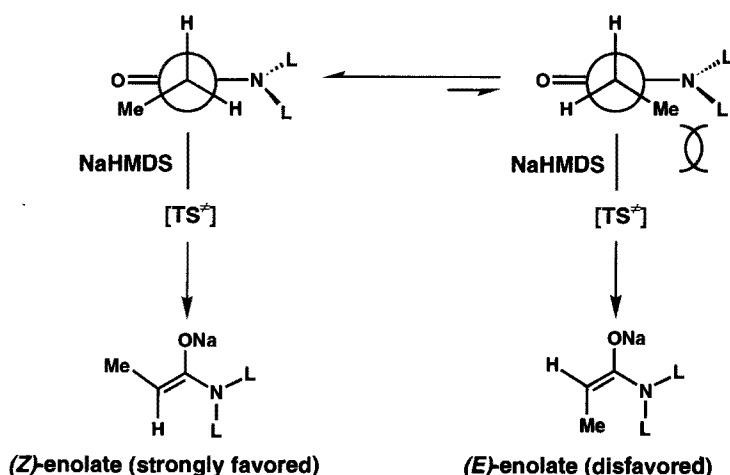
28.3 Total Synthesis

28.3.1 Synthesis of Spiroketal Subunit 6

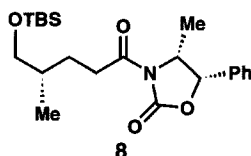
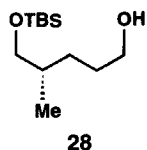
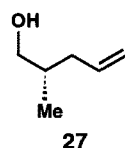
The synthesis of key intermediate **6** begins with the asymmetric synthesis of the lactol subunit, intermediate **8** (see Scheme 3). Alkylation of the sodium enolate derived from carboximide **21** with allyl iodide furnishes intermediate **26** as a crystalline solid in 82% yield and in >99% diastereomeric purity after recrystallization. Guided by transition state allylic strain conformational control elements^{5d} (see Scheme 4), the action of sodium bis(trimethylsilyl)amide on **21** affords chelated (*Z*)-enolate **25**. Chelation of the type illustrated in **25** prevents rotation about the nitrogen-carbon bond and renders



Scheme 3. Synthesis of lactol subunit **8**.

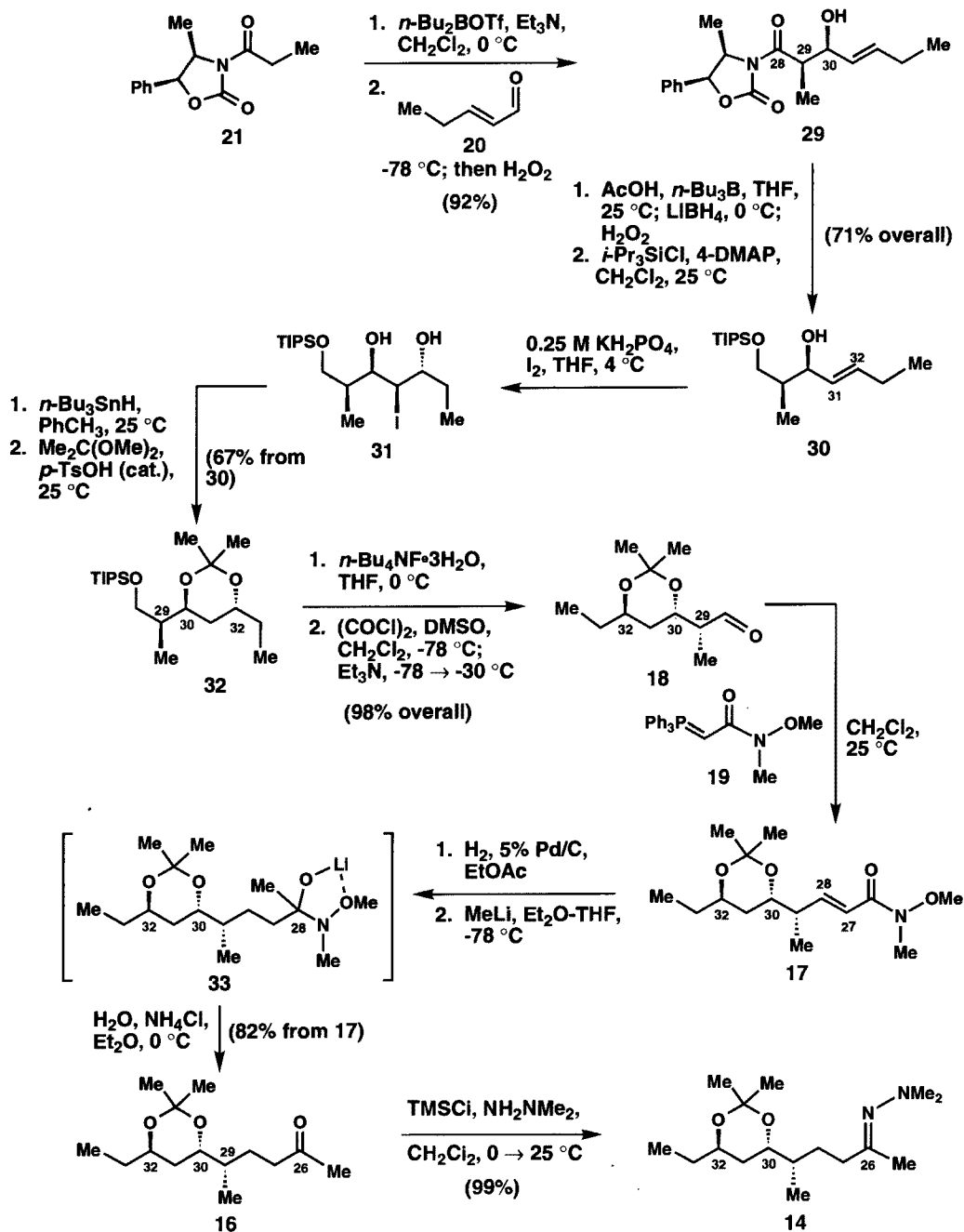


Scheme 4. Amide deprotonation allylic strain.

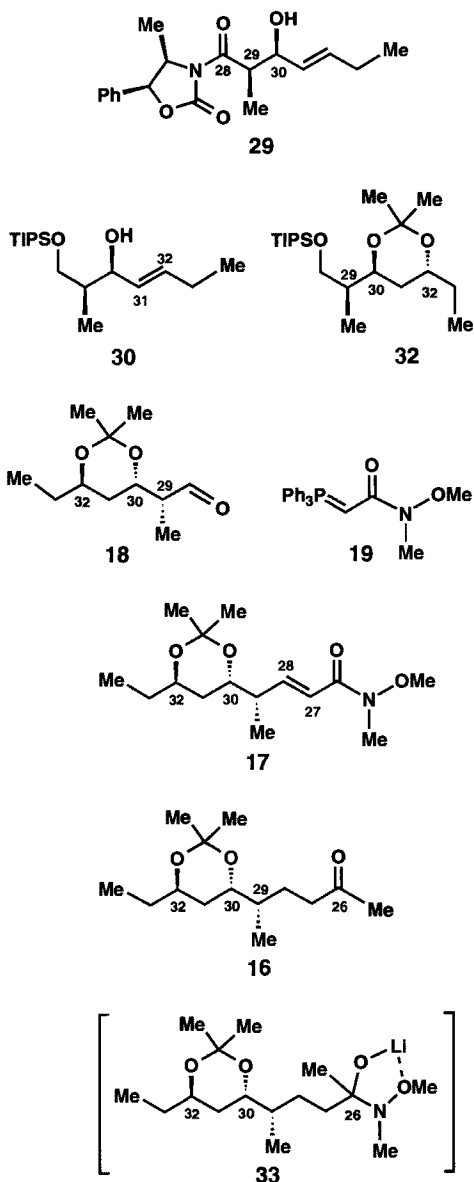


the *Re* enolate diastereoface substantially less hindered than the *Si* face. Hydrolytic removal of the norephedrine-derived chiral auxiliary in **26** with lithium hydroperoxide, followed by reduction of the resultant carboxylic acid with lithium aluminum hydride, furnishes primary alcohol **27**. After protection of this alcohol in the form of a *tert*-butyldimethylsilyl ether, hydroboration of the terminal olefin with 9-borabicyclo[3.3.1]nonane (9-BBN) gives **28** in an overall yield of 88 % from **26**. The task of oxidizing the primary alcohol in **28** to the corresponding carboxylic acid proved to be somewhat problematic because of the propensity of the product to lactonize under both acidic and basic conditions. Nevertheless, the action of potassium ruthenate in dilute potassium hydroxide on **28** accomplishes the desired oxidation and affords the desired carboxylic acid in a yield of 79 %. Treatment of this acid with pivaloyl chloride results in the formation of a mixed pivaloyl anhydride. This mixed anhydride is quite competent as an acylating agent and, in the presence of the lithiated norephedrine oxazolidone, it undergoes smooth conversion to the targeted lactol subunit, intermediate **8** (74 % from **28**).

Scheme 5 details the asymmetric synthesis of dimethylhydrazone **14**. The synthesis of this fragment commences with an Evans asymmetric aldol condensation between the boron enolate derived from **21** and *trans*-2-pentenal (**20**). *Syn* aldol adduct **29** is obtained in diastereomerically pure form through a process which defines both the relative and absolute stereochemistry of the newly generated stereogenic centers at carbons 29 and 30 (92 % yield). After reductive removal of the chiral auxiliary, selective silylation of the primary alcohol furnishes **30** in 71 % overall yield. The method employed to achieve the reduction of the C-28 carbonyl is interesting and worthy of comment. The reaction between tri-*n*-butylbor-



Scheme 5. Synthesis of intermediate 14.

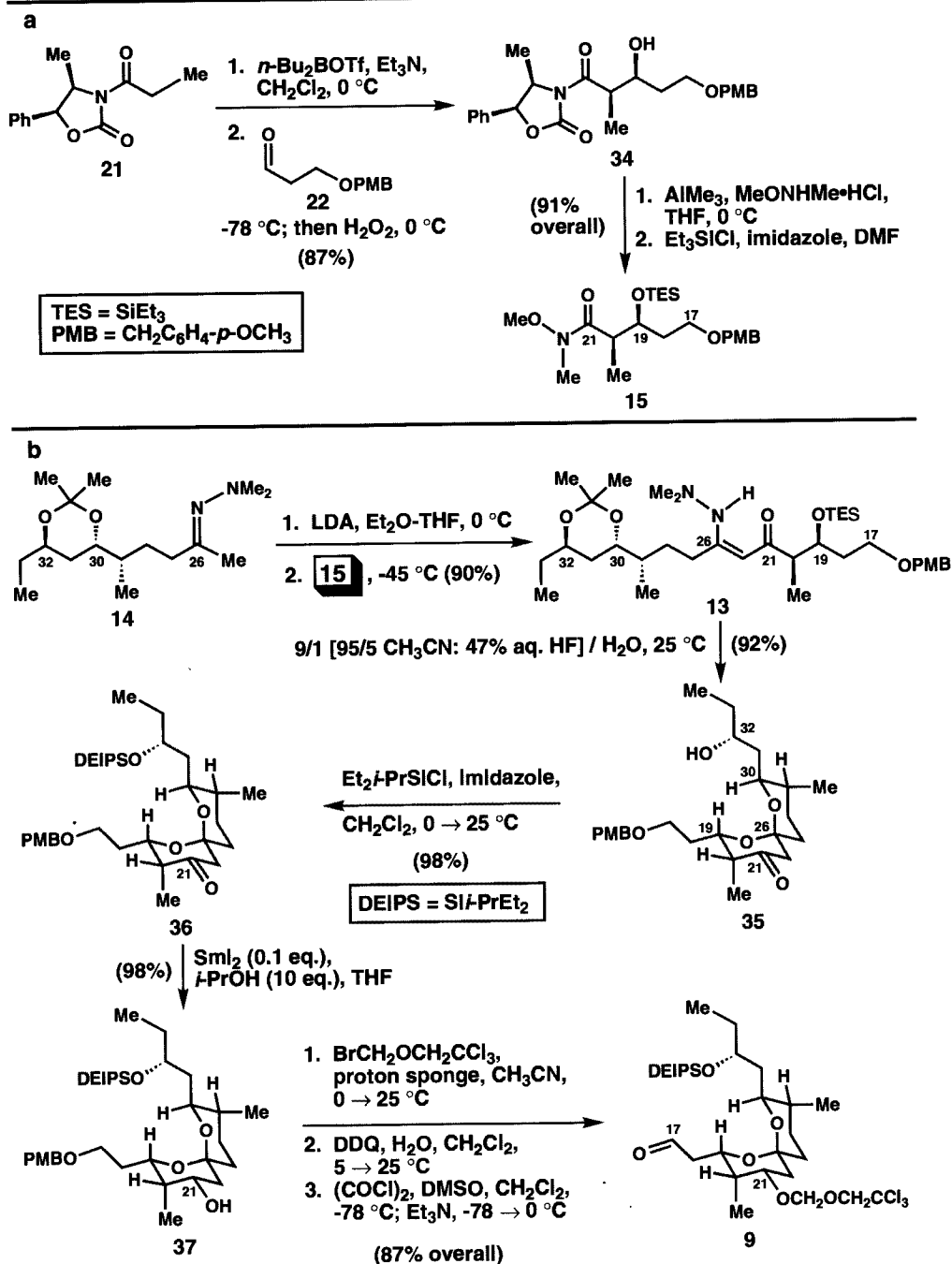


ane and glacial acetic acid affords dibutylboryl acetate which reacts with intermediate **29** to form a boron aldolate.^{9b} Internal coordination between the C-28 carbonyl oxygen and the Lewis acidic boron atom provides sufficient activation of the C-28 carbonyl for a reduction with lithium borohydride. Iodohydration¹⁹ of the C31-C32 double bond in **30**, followed sequentially by reductive cleavage of the carbon-iodine bond with tri-*n*-butyltin hydride and formation of the acetone ring, affords intermediate **32** in an overall yield of 67 %. The iodohydration reaction exhibits impressive diastereoselectivity (96:4) and accomplishes the introduction of the third and final stereocenter present in intermediate **14**. A straightforward two-step sequence of reactions accomplishes the formation of aldehyde **18** which undergoes homologation to **17** through a Wittig reaction with **19**. After saturation of the C27-C28 double bond in the conventional way with hydrogen over Pd-C, treatment with methyllithium accomplishes the formation of methyl ketone **16** through the intermediacy of the relatively stable complex **33**. The targeted hydrazone **14** forms smoothly when methyl ketone **16** is exposed to 1,1-dimethylhydrazine in the presence of trimethylsilyl chloride as a dehydrating agent.

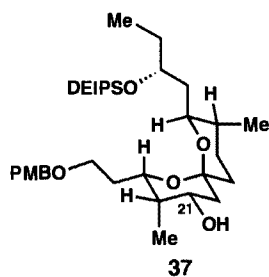
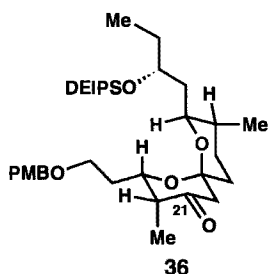
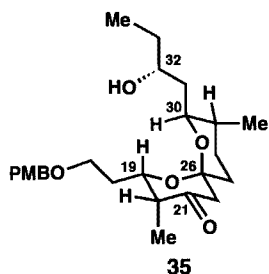
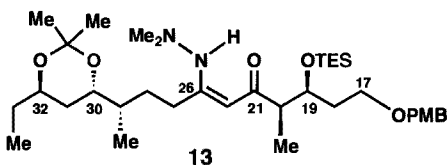
In general, the reaction of alkyl lithium reagents with amides to give ketones is not particularly effective because the product ketone is more electrophilic than the amide starting material and, therefore, more susceptible to nucleophilic attack. Once formed, the ketone would react much more quickly than the amide starting material with any remaining alkyl lithium reagent. However, *N*-methoxy-*N*-methylamides, also known as Weinreb amides,²⁰ are special. The addition of an alkyl lithium reagent to the carbonyl of a Weinreb amide affords a coordinated tetrahedral intermediate which is stable at low temperatures (see intermediate **33**). The desired ketone product **16** is revealed only after aqueous workup.

Scheme 6a presents the synthesis of fragment **15**. Intermediate **15** harbors two vicinal stereogenic centers, and is assembled in a very straightforward manner through the use of asymmetric aldol methodology. Treatment of the boron enolate derived from **21** with 3-[(*p*-methoxybenzyl)oxy]propanal (**22**) affords crystalline *syn* aldol adduct **34** in 87 % yield as a single diastereomer. Transamination to the *N*-methoxy-*N*-methylamide,²⁰ followed by silylation of the secondary hydroxyl group at C-19 with triethylsilyl chloride, provides intermediate **15** in 91 % yield.

Having retraced the remarkably efficient sequences of reactions which led to syntheses of key intermediates **14** and **15**, we are now in a position to address their union and the completion of the synthesis of the spiroketal subunit (Scheme 6b). Regiocontrolled deprotonation of hydrazone **14** with lithium diisopropylamide (LDA), prepared from diisopropylamine and halide-free methyllithium in ether, furnishes a metalloenamine which undergoes smooth acylation when treated with *N*-methoxy-*N*-methylcarboxamide **15** to give the desired vinylogous amide **13** in 90 % yield. It is instructive to take note of the spatial relationship between the



Scheme 6. Synthesis of intermediates 15 (a) and 9 (b).

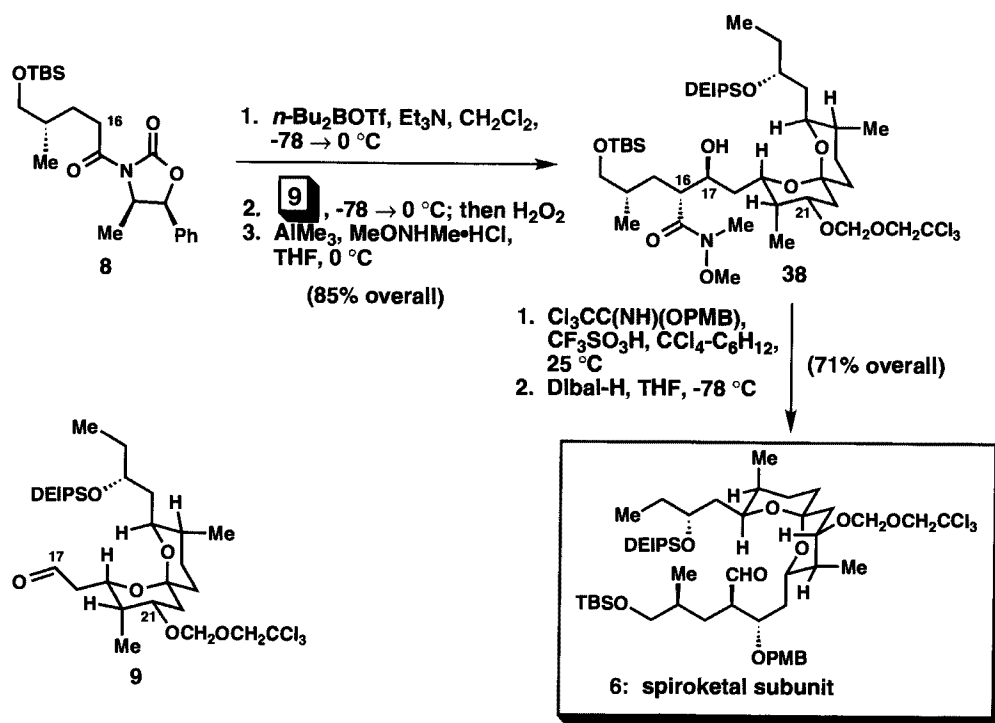


two oxygen atoms at positions 19 and 30 and C-26 of the vinylous amide in intermediate **13**. In a suitably acidic medium, it is conceivable that cleavage of both the acetonide ring and the triethylsilyl ether would occur to give a triol wherein the structural prerequisites for a spiroketalization reaction are satisfied. In the event, treatment of **13** with hydrofluoric acid in acetonitrile, buffered with a sufficient amount of water to reduce the acidity of the medium, unveils free hydroxyl groups at positions 19 and 30 which spontaneously converge, in an intramolecular fashion, on C-26 to give spiroketal keto alcohol **35** in 92 % yield. In one step, intermediate **13** is converted into **35** without recourse to a circuitous deprotection scheme.

Among the tasks remaining for the synthesis of the spiroketal subunit is the introduction of the C-21 equatorial hydroxyl group through reduction of the C-21 ketone carbonyl. Reduction of the keto group in **35** would afford a diol which may be difficult to differentiate. Thus, before **35** is reduced, the C-32 secondary hydroxyl group is protected in the form of a diethylisopropylsilyl (DEIPS) ether to give **36**. After a systematic survey of a number of reduction protocols, it was observed that an exceptionally diastereoselective reduction (65:1) of **36** to **37** could be achieved with a procedure developed by Kagan.²¹ Treatment of a solution of ketone **36** in THF with a catalytic amount of samarium diiodide²² and 10 equivalents of isopropanol effects a highly diastereoselective reduction of the C-21 ketone and furnishes the desired equatorial alcohol **37** in nearly quantitative yield (98 %). Kagan's procedure is a mild variant of the Meerwein-Ponndorf-Verley²³ reduction and, in this particular application, it is thought that the transannular axial spiroketal ether oxygen controls the stereochemical course of the reduction by assisting reagent delivery.

The synthesis of intermediate **9** from **37** (Scheme 6b) commences with the protection of the newly formed C-21 equatorial hydroxyl group in the form of a (2,2,2-trichloroethoxy)methoxy ether. The selection of this rather unusual protecting group is not arbitrary; it was anticipated that during the reductive elimination step in the Julia-Lythgoe¹⁷ coupling of the spiroketal subunit with the polyol glycoside subunit (see Scheme 2), sodium amalgam would also reductively cleave this protecting group. Treatment of a solution of **37** in acetonitrile with bromomethyl 2,2,2-trichloroethyl ether in the presence of proton sponge, followed sequentially by oxidative removal of the *p*-methoxybenzyl protecting group with DDQ and a Swern oxidation,²⁴ gives aldehyde **9** in an overall yield of 87 %.

A key step in the synthesis of the spiroketal subunit is the convergent union of intermediates **8** and **9** through an Evans asymmetric aldol reaction (see Scheme 2). Coupling of aldehyde **9** with the boron enolate derived from imide **8** through an asymmetric aldol condensation is followed by transamination with an excess of aluminum amide reagent to afford intermediate **38** in an overall yield of 85 % (see Scheme 7). During the course of the asymmetric aldol condensation

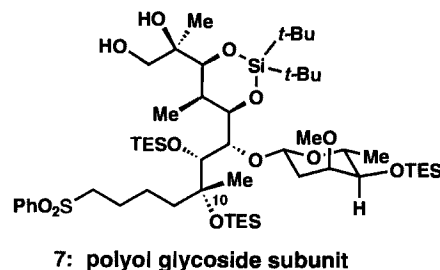


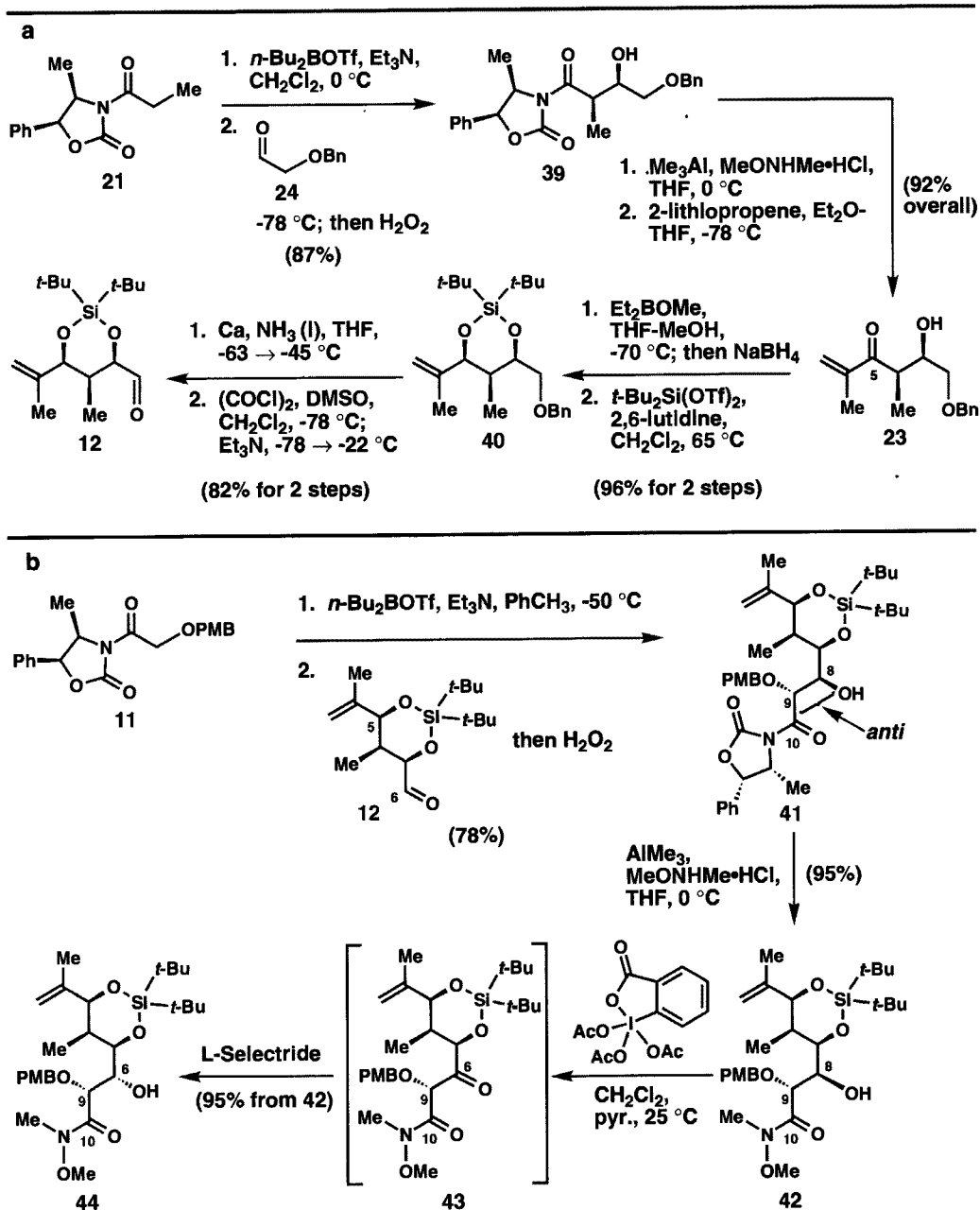
Scheme 7. Synthesis of spiroketal subunit **6**.

between intermediates **8** and **9**, a key bond between positions 16 and 17 is created and it is noteworthy that the desired aldol adduct is the only diastereoisomer formed. The completion of the synthesis of the spiroketal subunit now requires only two synthetic operations. Treatment of alcohol **38** with *p*-methoxybenzyl trichloroacetimidate in the presence of a catalytic amount of triflic acid, followed by reduction of the *N*-methoxy-*N*-methylamide with diisobutylaluminum hydride (Dibal-H), provides the key spiroketal subunit **6** in an overall yield of 71 %. An important virtue of *p*-methoxybenzyl protecting groups is that they are easily cleaved under mild conditions with DDQ.²⁵

28.3.2 Synthesis of Polyol Glycoside Subunit 7

The synthesis of the polyol glycoside subunit **7** commences with an asymmetric aldol condensation between the boron enolate derived from imide **21** and α -(benzyloxy)acetaldehyde (**24**) to give *syn* adduct **39** in 87 % yield and in greater than 99 % diastereomeric purity (see Scheme 8a). Treatment of the Weinreb amide,²⁰ derived in one step through transamination of **39**, with 2-lithiopropene furnishes enone **23** in an overall yield of 92 %. To accomplish the formation of the *syn* 1,3-diol, enone **23** is reduced in a chemo- and



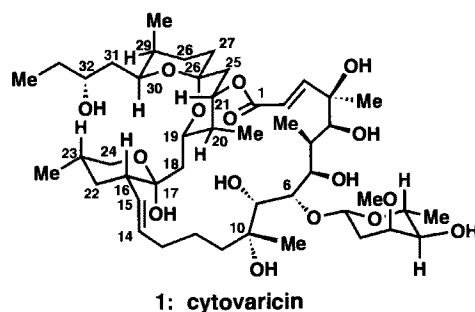


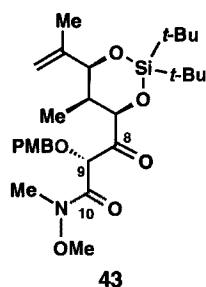
Scheme 8. Synthesis of intermediates 12 (a) and 44 (b).

stereoselective fashion through the use of the Sandoz procedure (NaBH_4 , Et_2BOMe).²⁶ It is presumed that the action of methoxy-diethylborane on **23** furnishes a boron chelate and that pre-existing asymmetry guides the stereochemical course of the reduction of the C-5 carbonyl with sodium borohydride. The desired *syn* 1,3-diol is formed with >100:1 diastereoselectivity. Simultaneous protection of both hydroxyl groups in the form of a cyclic di-*tert*-butylsilylene ketal (see **40**) followed by removal of the benzyl protecting group and a Swern oxidation provides aldehyde **12** in a overall yield of 79% from intermediate **23**.

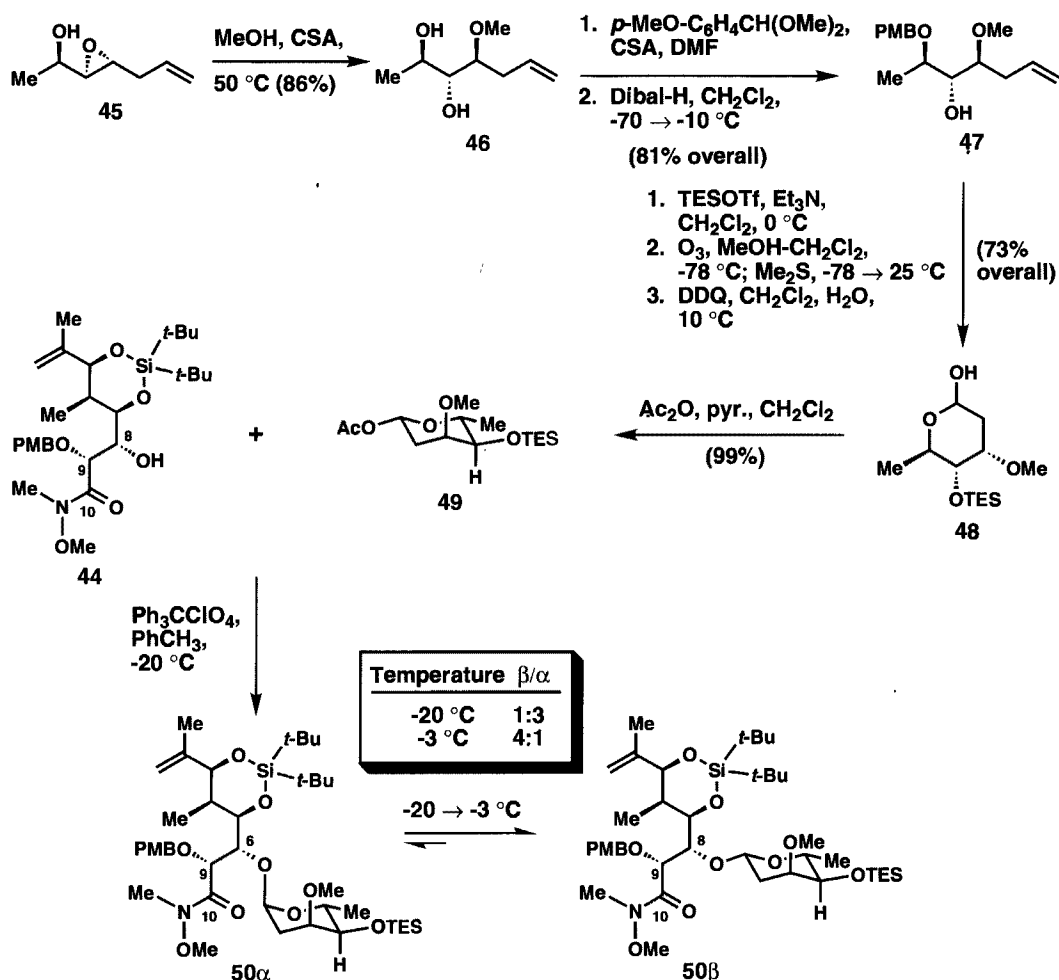
A digression is in order at this juncture. An elegant feature of Evans's design is the recognition that it could be possible to facilitate the key macrocyclization event by constraining the ring torsion angles of the macrocycle to those found in the X-ray structure of cytovaricin (**1**). It was recognized that such conformational ordering could be achieved through the application of cyclic protecting groups in the elaboration of the C4-C10 polypropionate region of the macrolide (see Scheme 2). Although the 1,2- and 1,3-diol relationships present in this portion of cytovaricin offer several bridging options, it was decided to bridge only those pairs of hydroxyl groups which are oriented away from the interior of the ring and are as close to *syn* planarity as possible. An analysis of the X-ray structure of cytovaricin revealed that the C5-C7 and C8-C10 1,3-diol relationships appear to satisfy these two requirements; the other 1,2- and 1,3-diol dihedral relationships deviate too significantly from *syn* planarity. The decision to glycosidate the C-8 hydroxyl group prior to macrocyclization sacrificed the C8-C10 bridging option, and the decision to employ silicon-based protecting groups led to the use of a di-*tert*-butylsilylene protecting group bridging the C5-C7 1,3-diol.

A distinguishing attribute of the Evans asymmetric aldol process is that reaction stereoselection is, with few exceptions, completely controlled by the enolate chirality, regardless of the chirality of the aldehyde. Even when pitted against the inherent diastereofacial preference of an aldehyde substrate, the chiral auxiliary of the enolate prevails and dictates the stereochemical course of the aldol reaction. The latter observation has naturally expanded the scope of the Evans asymmetric aldol reaction and it highlights the following virtue of the reagent-control strategy for stereochemical control. *Through the application of powerful enantiomerically pure reagents or catalysts, it is often possible to overwhelm the modest diastereofacial preferences exhibited by a chiral substrate molecule.*^{4b} It was, therefore, very surprising to find that the asymmetric aldol condensation between aldehyde **12** and the boron enolate derived from **11** proceeds with complete stereocontrol to yield the *anti* aldol adduct **41** as a single diastereomer in 78% yield (see Scheme 8b)! The unanticipated reversal of stereochemistry in this reaction was unprecedented with this chiral enolate reagent. It appears that the chiral auxiliary defines the stereocenter at C-9, while the inherent Felkin-Anh²⁷ diastereofacial bias of the chiral aldehyde guides the formation of the





C-8 stereocenter. This obstacle was not trivial because all efforts to override the inherent diastereofacial preference of aldehyde **12** through an aldol bond construction were thwarted. One solution to this problem would take full advantage of the inherent diastereofacial bias of a trigonal carbon atom at C-8. Accordingly, Dess-Martin oxidation²⁸ of the transaminated *anti* aldol adduct **42**, followed immediately by *in situ* reduction of the newly formed β -ketoamide **43** with lithium tri-*sec*-butylborohydride (L-Selectride), gives the desired alcohol **44** as a single diastereomer in an excellent overall yield of 95 %. Despite the intermediacy of an oxygenated 1,3-dicarbonyl species (see **43**), epimerization at C-9 is not observed. It is presumed that allylic 1,3-strain²⁹ sufficiently reduces the acidity of the C-9



Scheme 9. Synthesis of β -acetoxo glycoside **49** and glycosidation of **44** to give **50 β** .

methine hydrogen to the extent that epimerization at C-9 does not occur (see Figure 1).

Scheme 9 presents the synthesis of the D-cymarose sugar derivative **49**. Exposure of epoxy alcohol **45** (the product of a Sharpless asymmetric epoxidation³⁰ of the corresponding allylic alcohol) to methanol and camphorsulfonic acid (CSA) at 50 °C provides diol methyl ether **46** in 86 % yield. Simultaneous protection of the vicinal hydroxyl groups in the form of a *p*-methoxybenzylidene acetal, followed by regioselective (8:1) acetal cleavage with diisobutylaluminum hydride (Dibal-H), gives the desired *p*-methoxybenzyl (PMB) ether alcohol **47** in an overall yield of 81 %. Triethylsilylation of the secondary hydroxyl group is followed sequentially by oxidative cleavage of the terminal olefin with ozone and removal of the PMB protecting group with DDQ to give crystalline lactol **48** as a mixture of anomers in 73 % yield. Finally, acetylation of the anomeric hydroxyl group with acetic anhydride affords, in a yield of 99 %, β -acetoxy glycoside **49**. It is noteworthy that the desired equatorial glycoside **49** is formed exclusively and is suitably activated for a glycosidation reaction.

The manner in which the stereochemical course of glycosidation reactions is customarily controlled involves the use of neighboring group active glycosyl donors. After activation of the anomeric carbon atom, a suitable heteroatom substituent in the 2-position of the glycosyl donor guides the stereochemical course of the glycosidation event. Several efficient protocols have been developed for the purpose of achieving sterecontrolled glycosidic bond constructions and these have been amply reviewed.³¹ D-Cymarose is a 2-deoxysugar and acetoxy glycoside **49** does not possess a heteroatom substituent of any kind in the 2-position. Nevertheless, a β -selective glycosidation of the C-8 hydroxyl group in intermediate **44** can be achieved using a modification of Mukaiyama's protocol³² (Scheme 9). In the event, treatment of a cooled (–20 °C) solution of alcohol **44** and acetoxy glycoside **49** (see Scheme 9) in toluene with a catalytic amount of trityl perchlorate, followed by warming of the heterogeneous mixture to –3 °C, provides a 4:1 equilibrium mixture in favor of the desired β -glycoside **50 β** . If the temperature is maintained at –20 °C, a rapid reaction takes place to afford a 1:3 mixture of glycosides favoring the undesired axial anomer **50 α** . Interestingly, warming of the reaction mixture to –3 °C induces an anomer equilibration to give **50 β** in a 4:1 mixture with **50 α** . The undesired axial anomer **50 α** can be recovered and resubmitted to the reaction conditions to give a 4:1 mixture of glycosides favoring **50 β** . In this manner, **50 β** can be obtained in a yield of 70 %.

Although trityl perchlorate is used to accomplish the glycosidation of the C-8 hydroxyl in **44** with acetoxy glycoside **49**, control experiments have demonstrated that no reaction takes place in the presence of 4 Å molecular sieves or 2,6-di-*tert*-butylpyridine. This observation suggests that the actual catalyst is not trityl perchlorate, but perchloric acid. Consistent with this conclusion is the observation that catalytic amounts of a strong Brønsted acid such as triflic or perchloric acid can catalyze the glycosidation of **44** with **49** in the absence of trityl perchlorate.

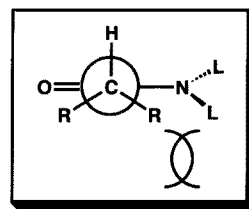
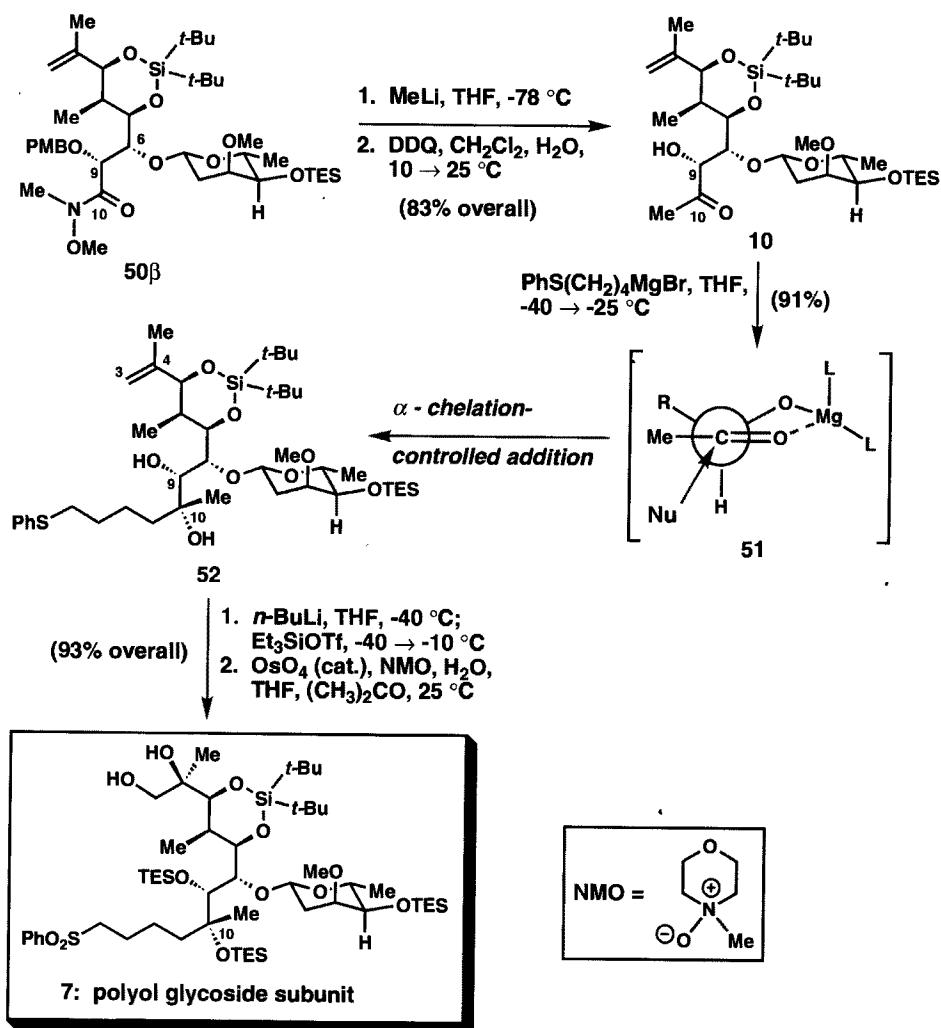


Figure 1. Attenuation of C-H acidity by allylic 1,3-strain.



Scheme 10. Synthesis of polyol glycoside subunit **7**.

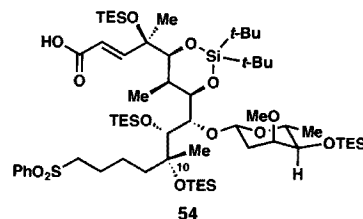
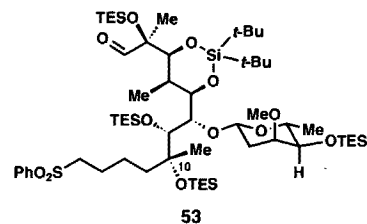
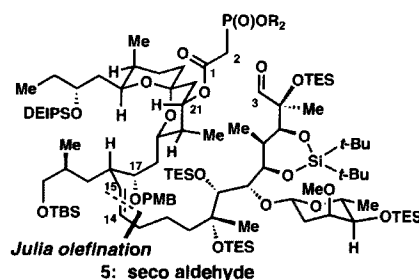
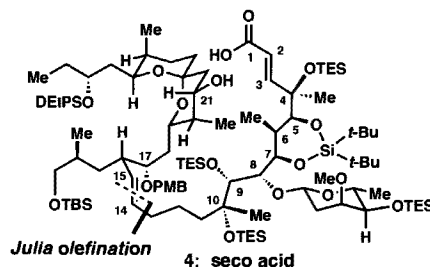
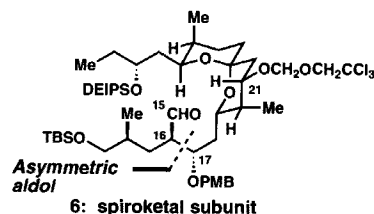
The completion of the synthesis of the polyol glycoside subunit **7** requires construction of the fully substituted stereocenter at C-10 and a stereocontrolled dihydroxylation of the C3-C4 geminally-disubstituted olefin (see Scheme 10). The action of methyllithium on *N*-methoxy-*N*-methylamide **50β** furnishes a methyl ketone which is subsequently converted into intermediate **10** through oxidative removal of the *p*-methoxybenzyl protecting group with DDQ. Intermediate **10** is produced in an overall yield of 83% from **50β**, and is a suitable substrate for an α -chelation-controlled carbonyl addition reaction.¹⁸ When intermediate **10** is exposed to three equivalents of

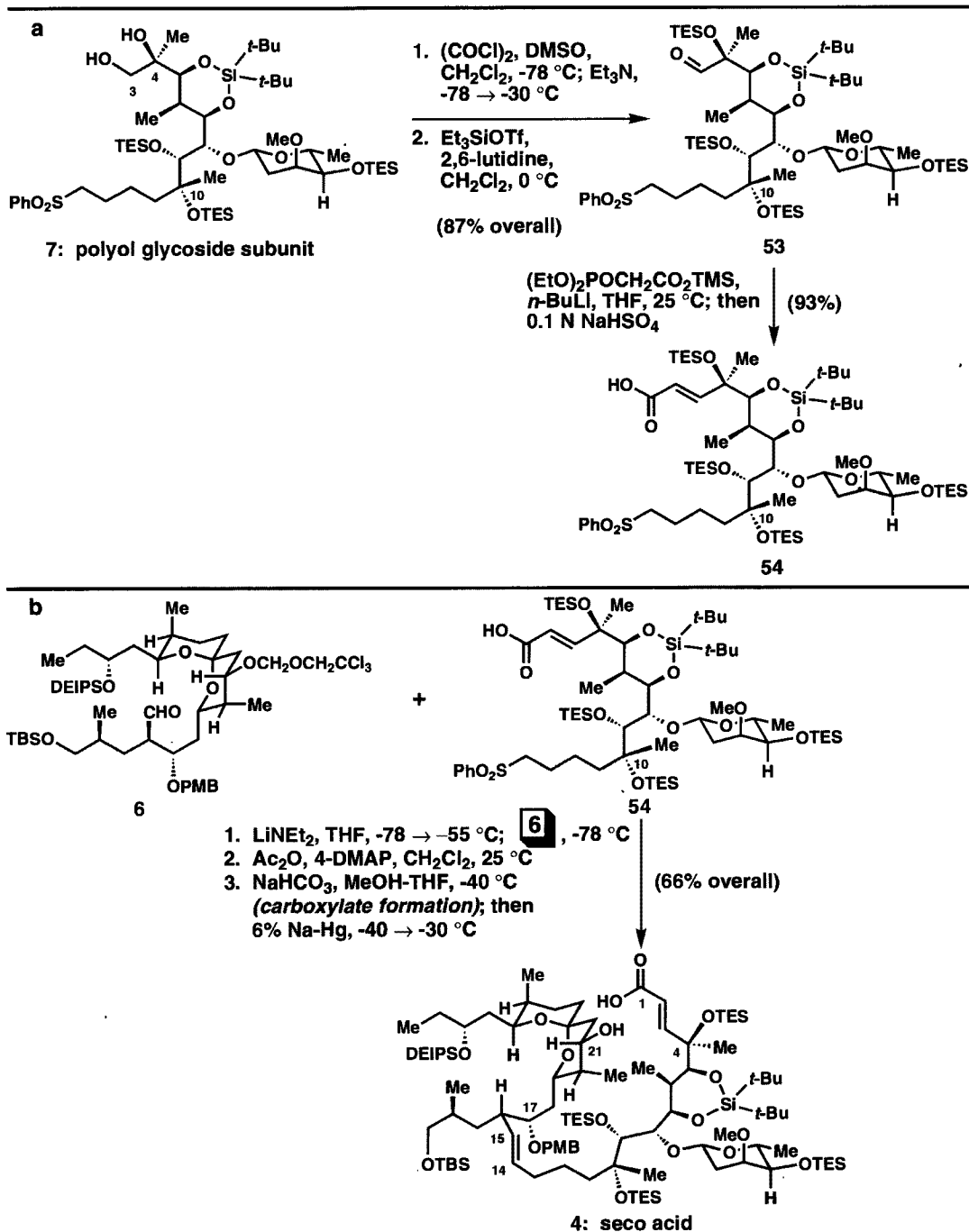
the Grignard reagent derived from 1-bromo-4-phenylthio-butane, a smooth α -chelation-controlled addition to the C-10 ketone carbonyl takes place and provides diol **52** as the only detectable diastereomer in 91% yield. After consumption of one equivalent of the Grignard reagent through an acid-base reaction with the free hydroxyl group at C-9 in **10**, a five-membered chelate (**51**) is formed. It is instructive to note that one ketone diastereoface in **51** is considerably more hindered than the other. The rigid five-membered chelate in **51** induces the nucleophilic addition to proceed across the less hindered *Re* face to give intermediate **52**. In this way, the stereogenic center at C-9 controls the emergence of a new stereogenic center at C-10; stereogenicity at C-9 is *communicated*,^{4a} through the intermediacy of a rigid chelate, to the adjacent C-10 position. After protection of both hydroxyl groups in **52** in the form of triethylsilyl ethers, the C3-C4 olefin is dihydroxylated, in a completely diastereoselective fashion, with a catalytic amount of OsO₄ and excess *N*-methylmorpholine *N*-oxide (NMO) to give the polyol glycoside subunit **7** in 93% yield. Usefully, dihydroxylation of the C3-C4 olefin is accompanied by oxidation of the thiophenyl moiety to the corresponding sulfone.

Sulfone **7** is a versatile synthetic intermediate. Through a Julia-Lythgoe coupling reaction,¹⁷ it ought to be possible to bring about a convergent union of **7** and aldehyde **6** with concomitant formation of a double bond between carbons 14 and 15 (see Scheme 2). Seco acid **4** and seco aldehyde **5** could then be elaborated in short order so that both macrolactonization and carbomacrocyclization options could be tested, respectively.¹⁶ Because the desired 22-membered lactone could never be obtained in a yield greater than 35% from a Horner-Wadsworth-Emmons cyclization of seco aldehyde **5**, all efforts were devoted to the development of the macrolactonization option.

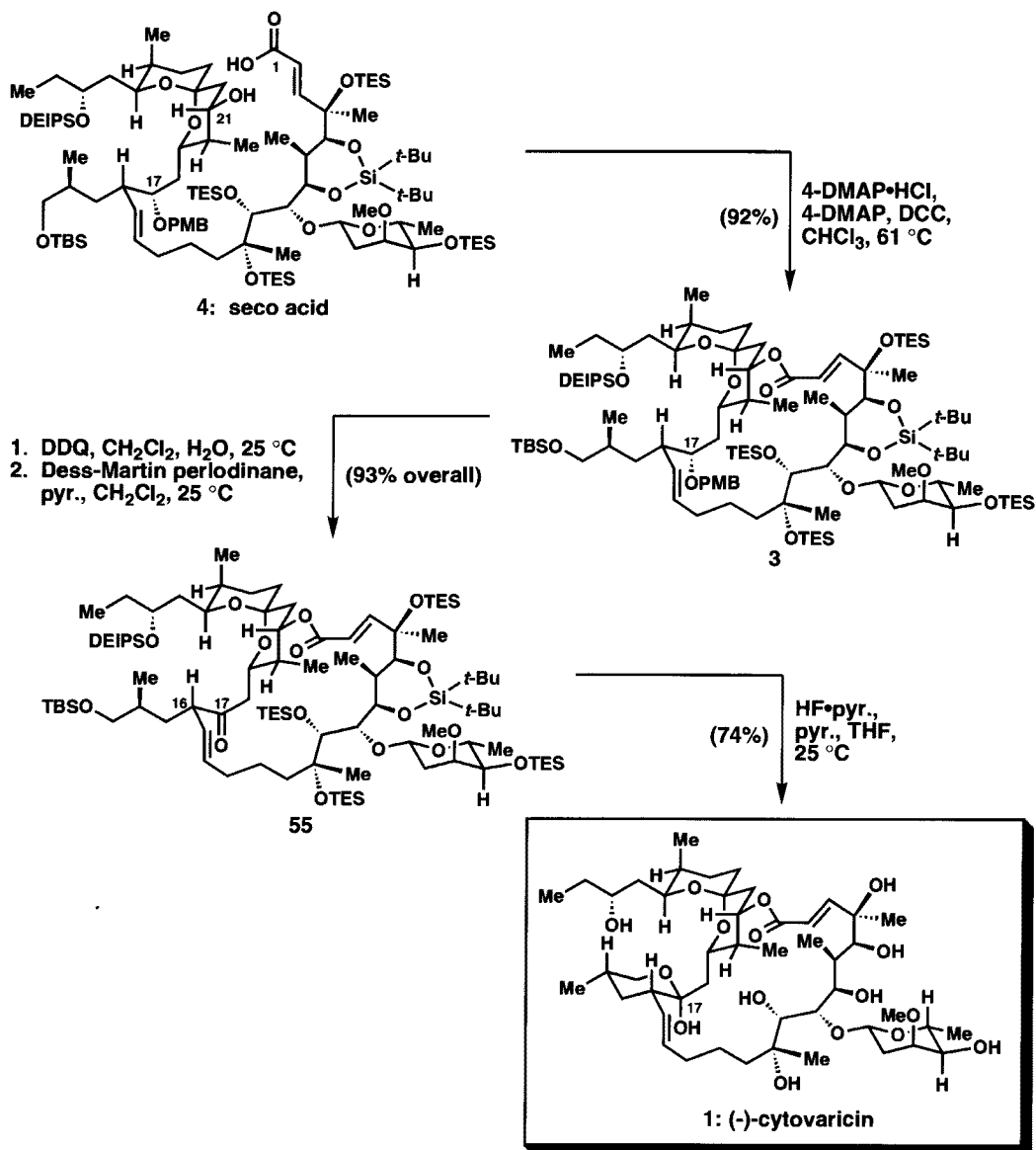
28.3.3 Synthesis of Seco Acid **4** and Completion of the Total Synthesis of Cytovaricin

In the interest of convergency, it was decided to construct the α,β -unsaturated acid moiety prior to the Julia coupling with aldehyde **6** (see Scheme 11a). Swern oxidation of the primary hydroxyl group at C-3 in **7** to the corresponding aldehyde, followed immediately by triethylsilylation of the C-4 tertiary hydroxyl group, gives sulfone aldehyde **53** in an overall yield of 87%. The desired α,β -unsaturated acid **54** could then be obtained in an excellent yield of 93% through Wittig homologation of **53**. Treatment of sulfone acid **54** with 2.1 equivalents of lithium diethylamide results in the formation of a dianion which reacts smoothly with aldehyde **6** to give a nearly equimolar mixture of β -hydroxy sulfones (see Scheme 11b). Acetylation of the mixture of β -hydroxy sulfones with acetic anhydride then furnishes a mixture of acetoxy sulfones in quantitative yield. Treatment of the mixture of acetoxy sulfones with an excess

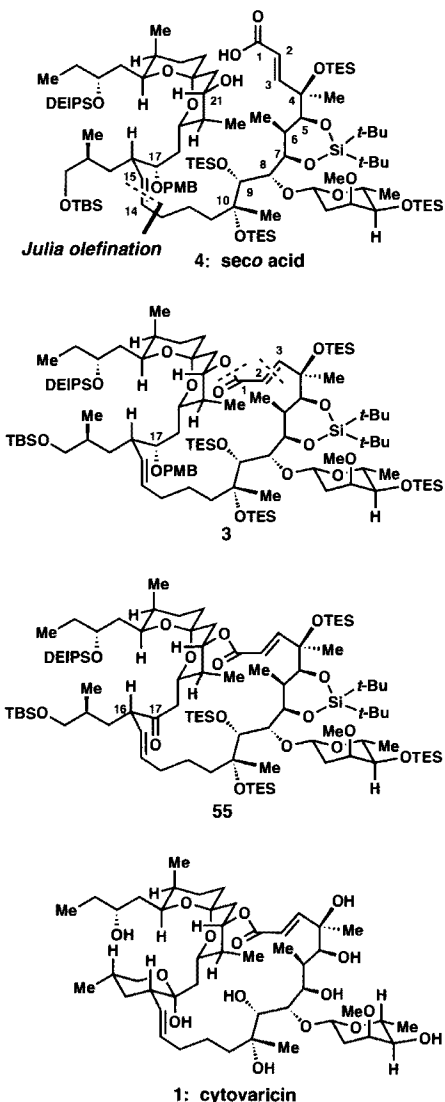




Scheme 11. Synthesis of intermediate **54** (a) and coupling of intermediates **6** and **54** (b).



Scheme 12. Synthesis of (-)-cytovaricin (1).



of sodium bicarbonate in a mixture of methanol and THF at -40°C accomplishes the conversion of the carboxylic acid moiety to the sodium carboxylate. This reaction was performed to prevent deconjugative cleavage of the C4-oxygen bond under the strongly reducing conditions necessary to effect elimination of the β -acetoxy sulfone. When the mixture of β -acetoxy sulfones is exposed to a large excess of pulverized 6% sodium amalgam, reductive elimination of the acetoxy sulfone to the requisite *trans* double bond (C14-C15) and cleavage of the C-21 (2,2,2-trichloroethoxy)methoxy protecting group both take place to afford the desired seco acid **4** in an overall yield of 66%.

We have reached a critical stage in the synthesis. Through a Julia-Lythgoe *trans* olefination reaction,¹⁷ two intermediates representing the "left- and right-hand" sectors of cytovaricin have been joined to give the key macrolactonization substrate, seco acid **4**. Gratifyingly, *in situ* activation of the C-1 carboxyl group in **4** using Keck's carbodiimide macrocyclization methodology³³ is attended by smooth internal esterification of the C-21 equatorial hydroxyl group to give macrocycle **3** in an excellent yield of 92% (see Scheme 12). Oxidative cleavage of the C-17 *p*-methoxybenzyl ether followed by Dess-Martin oxidation of the resultant secondary hydroxyl group provides β,γ -unsaturated ketone **55** in an overall yield of 93%. It is noteworthy that neither epimerization at C-16 nor olefin conjugation occurs under these conditions. Finally, treatment of **55** with buffered pyridinium hydrofluoride at 25°C for 60 hours accomplishes the removal of all seven silicon protecting groups and provides (-)-cytovaricin (**1**) in a yield of 74%. It is interesting to note that partially desilylated intermediates which are produced during the course of the conversion of **55** to **1** are significantly more polar than the natural product. This observation suggests that a hydrogen-bonding network may be present in cytovaricin which is disrupted in partially protected intermediates. The elegant asymmetric total synthesis of the macrolide, cytovaricin, is now complete.

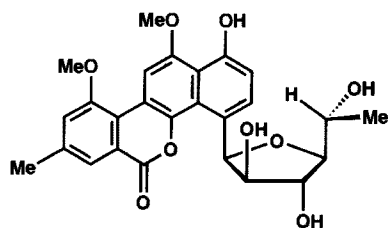
28.4 Conclusion

This highly convergent synthesis amply demonstrates the utility of Evans's asymmetric aldol and alkylation methodology for the synthesis of polypropionate-derived natural products. By virtue of the molecular complexity and pronounced lability of cytovaricin, this synthesis ranks among the most outstanding synthetic achievements in the macrolide field.

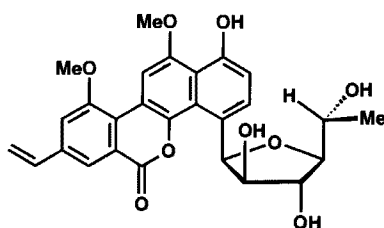
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1: gilvocarcin M



2: gilvocarcin V

K. Suzuki (1992, 1994)

Gilvocarcin M and Gilvocarcin V

29.1 Introduction

Various strains of *Streptomyces* produce a large number of natural products distinguished by a carbon–carbon bond between a tetracyclic aromatic sector and a unique carbohydrate domain.¹ The natural products constituting the gilvocarcin family of aryl C-glycosides² have engendered much interest by virtue of their novel structures and because some of the members exhibit remarkable antitumor activity with exceptionally low toxicity. For example, gilvocarcin V (**2**) is a competent DNA intercalator that induces single-strand cleavage of duplex DNA upon activation with low-energy light.³ Interestingly, the potent antitumor activity of gilvocarcin V (**2**) is not shared by the closely related gilvocarcin M (**1**). Although the tetracyclic aromatic substructures of both compounds are very similar, the vinyl substituent attached to C-8 (gilvocarcin numbering) in **2** plays an indispensable role in the DNA cleavage process.

The aglycon of gilvocarcin V, defucogilvocarcin V, itself a naturally occurring compound, has been the target of numerous successful and very interesting synthetic studies.^{4,5} However, the development of viable synthetic pathways to the intact aryl C-glycosides has been hampered by difficulties associated with the regio- and stereoselective construction of the crucial C-glycosidic bond.⁶ Indeed, the necessity of effecting a contrasteric (i.e. 1',2'-*cis* and 1',4'-*cis*) C-glycosylation is a most intimidating prerequisite for a gilvocarcin total synthesis.

In 1992, Suzuki and coworkers disclosed the total synthesis of (+)-gilvocarcin M, the enantiomer of naturally occurring (–)-gilvo-

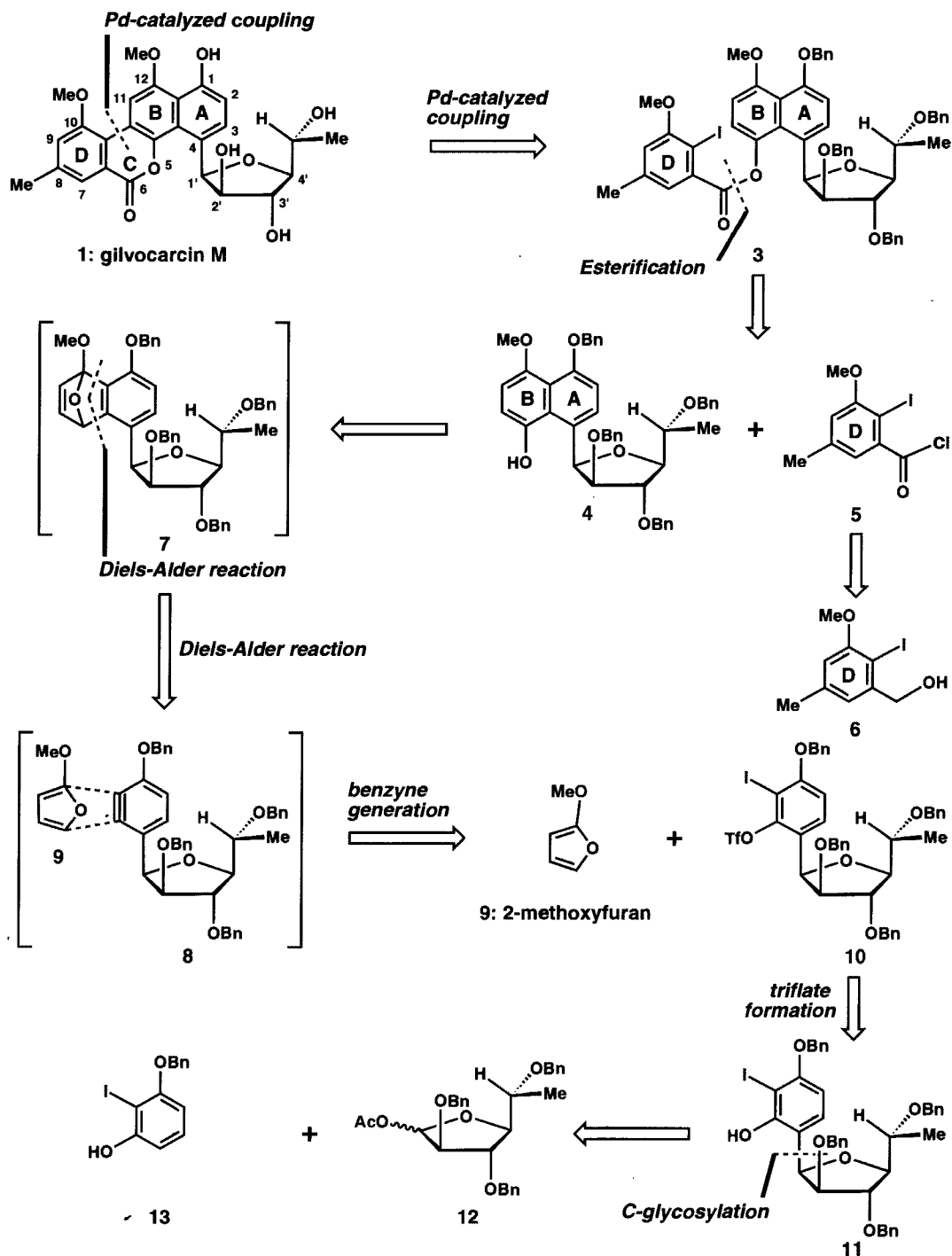
carcin M (**1**).^{7a} This outstanding synthesis was praised for its brevity and elegance,⁸ and it unequivocally established the absolute configuration of natural gilvocarcin M as shown in **1**. This synthesis can probably be regarded as the crowning achievement of a very successful research program which also demonstrated the utility of the hafnocene dichloride/silver perchlorate system ($\text{Cp}_2\text{HfCl}_2\text{--AgClO}_4$) as a promoter for aryl C-glycosylation reactions.⁹ A few years after their original disclosure, Suzuki *et al.* reported total syntheses of gilvocarcins M (**1**) and V (**2**), each in its naturally occurring stereochemical form.^{7b} This chapter addresses Suzuki's elegant syntheses of these two molecules.

29.2 Retrosynthetic Analysis and Strategy

The general features of Suzuki's synthesis of (–)-gilvocarcin M (**1**) are outlined retrosynthetically in Scheme 1. On the basis of the elegant synthesis of the gilvocarcin aglycon by Martin *et al.*,^{4b} it was projected that the carbon–carbon bond joining rings B and D of the aromatic sector in **1** could be constructed through a palladium-mediated cyclization of aryl iodide **3**. This particular cyclization strategy is very attractive because it could simultaneously create the crucial B–D bond and complete the annulation of ring C in a single operation. In addition, the requisite cyclization substrate **3** is also amenable to a very productive retrosynthetic maneuver: Cleavage of the ester linkage in **3** provides compounds **4** and **5** as potential precursors. Thus, in the synthetic direction, the combination of convergent acylation and Pd-induced cyclization reactions could accomplish the introduction of rings C and D of the natural product.

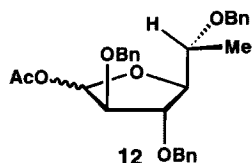
Acid chloride **5** is readily available from the known benzylic alcohol **6**,^{4e} but intermediate **4** is still rather complex. It was recognized that compound **4** could conceivably be formed in one step from 2-methoxyfuran (**9**)¹⁰ and iodotriflate **10**. The latter compound was designed with the expectation that it could be converted to benzyne **8**,¹¹ a highly reactive species that could be intercepted in an intermolecular Diels–Alder reaction with 2-methoxyfuran (**9**) to give **7**. The intermediacy of **7** is expected to be brief, for it should undergo facile conversion to the aromatized isomer **4** either *in situ* or during workup.

Retrosynthetic cleavage of the aryl C-glycosidic bond in **11**, the projected precursor of **10**, reveals the known D-fucose derived acetate **12**¹² and phenol **13** as potential starting materials for the synthesis. Compound **12**, equipped with an anomeric acetoxyl function, could serve as a glycosyl donor in a C-glycosylation reaction with **13**. This concise synthetic strategy is thus highly convergent. Schemes 2–8 detail the execution of this plan and the achievement of the first total synthesis of gilvocarcins M (**1**) and V (**2**).



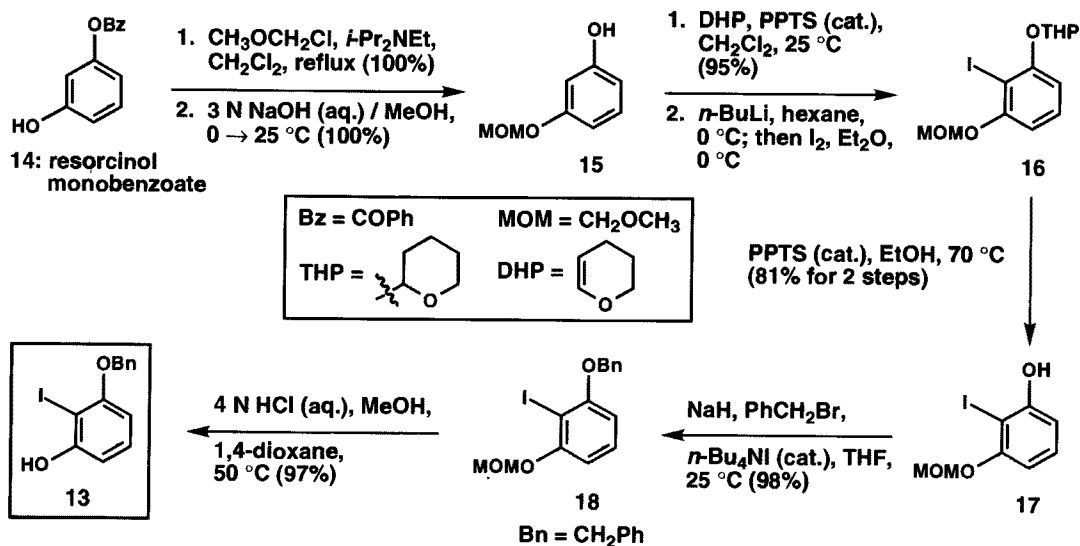
Scheme 1. Retrosynthetic analysis of gilvocarcin M (1).

29.3 Total Synthesis

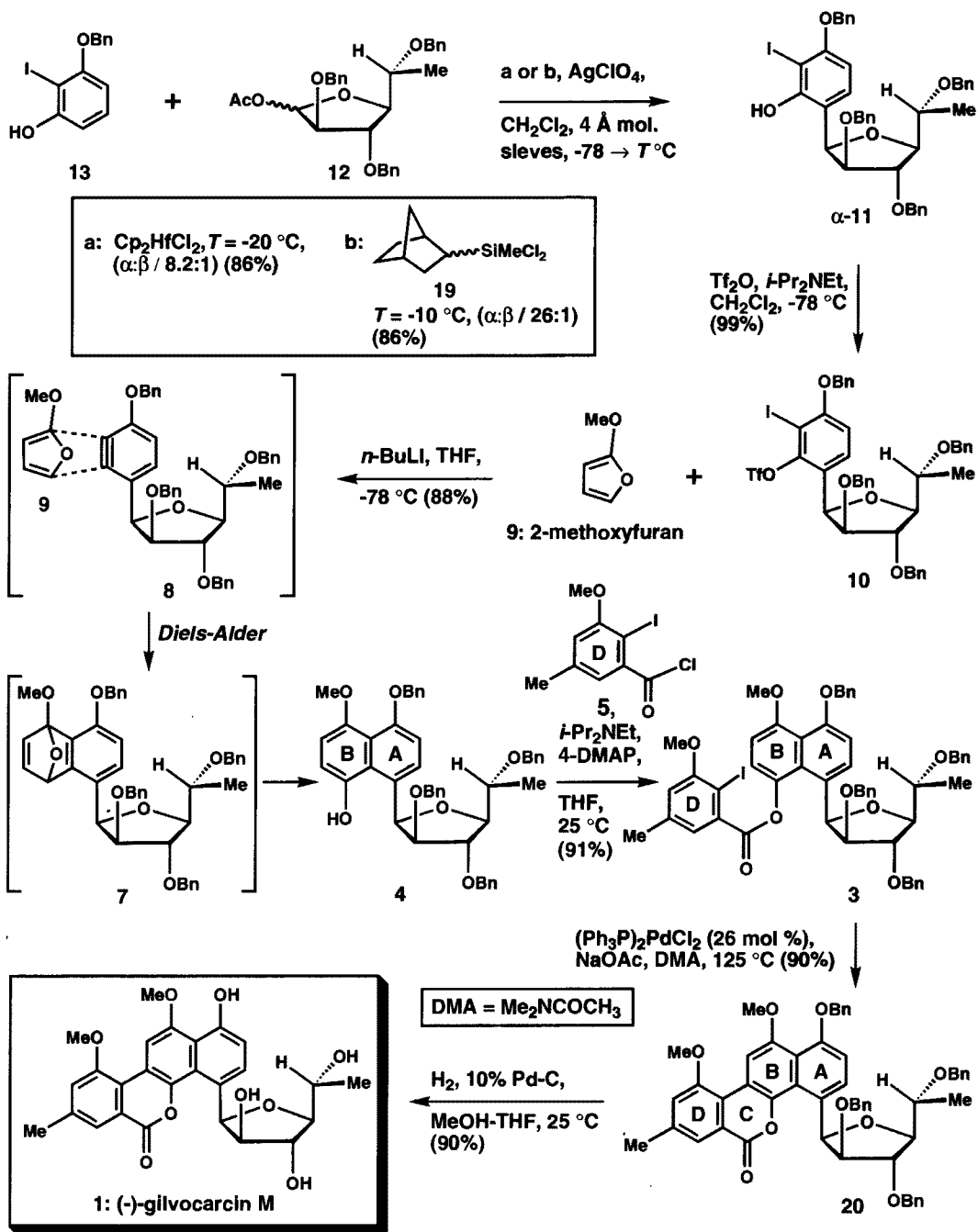


The two building blocks for the synthesis, compounds **12** and **13**, are both readily available. Benzyl protected D-fucofuranosyl acetate (**12**) can be prepared via a known protocol,¹² and the iodoresorcinol derivative **13** can be synthesized in short order from commercially available resorcinol monobenzoate (**14**) (see Scheme 2). The latter compound is an ideal starting material because the two oxygens are already differentiated. The reaction sequence employed to achieve the conversion of **14** to **13** is very straightforward and does not warrant any special comment. It is, however, instructive to address the important role that the iodine atom will play in this synthesis; although the iodine atom in compound **13** is not expressed in the gilvocarcins, it will, at a later stage, permit the generation of the reactive benzyne **8**.

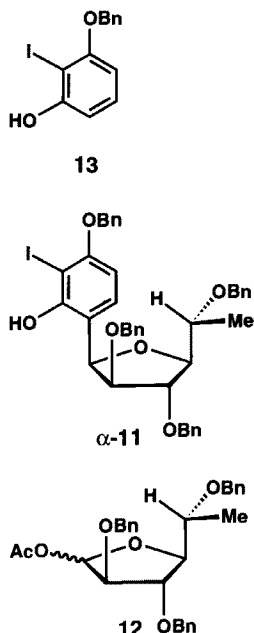
The convergent union of compounds **12** and **13** through a C-glycosidic bond is the most challenging step of the synthesis. As we have already mentioned, a contrasteric C-glycosylation of **13** must be achieved. In the event, treatment of a solution of compounds **12** and **13** in CH_2Cl_2 with the $\text{Cp}_2\text{HfCl}_2\text{-AgClO}_4$ glycosylation promoter at $-78 \rightarrow -20^\circ\text{C}$ (condition a) results in the formation of the desired α -C-glycoside α -**11** in 86% yield ($\alpha:\beta$ ca. 8.2:1) (see Scheme 3). At first glance, it might appear that the position *ortho* to



Scheme 2. Synthesis of intermediate **13**.



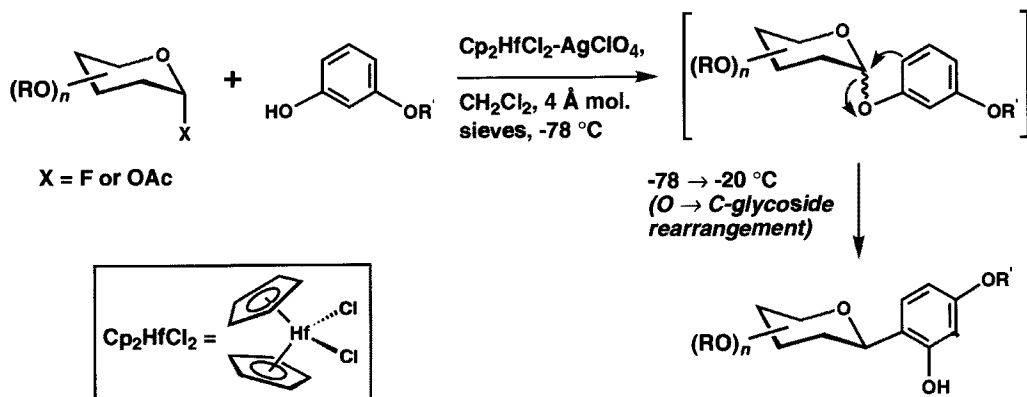
Scheme 3. Synthesis of (-)-gilvocarcin M (1).



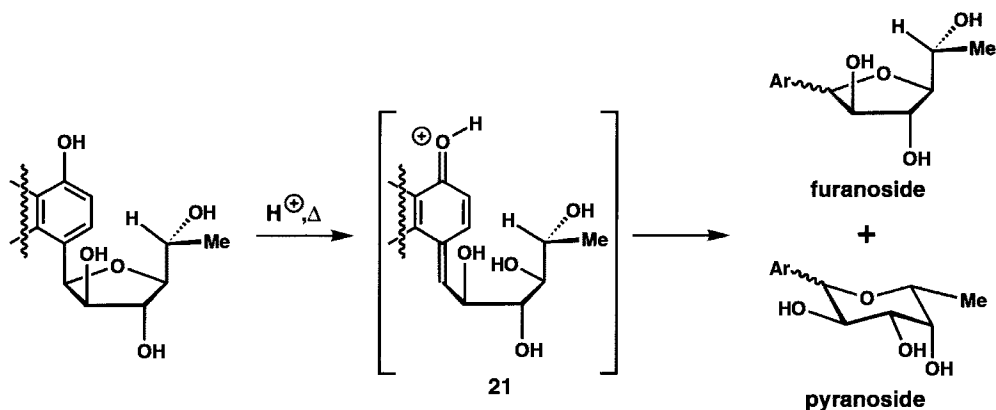
the hydroxyl group in **13** is glycosylated directly in this reaction. As it turns out, however, it is the free phenolic hydroxyl in **13** that is glycosylated first at -78°C ; upon warming to -20°C , the initially formed *O*-glycoside participates in an *O* \rightarrow *C*-glycoside rearrangement⁹ (see Scheme 4) to give α -aryl *C*-glycoside α -**11** as the major stereoisomer. It is also noteworthy that the desired *ortho* *C*-glycosylated adduct is produced with complete regioselectivity.

Silver perchlorate is an essential additive in this reaction. The chlorophilic silver ion converts hafnocene dichloride into an electron-deficient hafnocene complex.^{9f} Achievement of high α -stereoselectivity in the glycosylation reaction critically depends on the use of AgClO_4 in this reaction. Interestingly, the combination of the novel silane **19** and AgClO_4 (condition b, Scheme 3) effects a highly stereoselective and completely regioselective coupling of compounds **12** and **13**, providing a 26:1 ratio of stereoisomeric glycosides in favor of the desired α -**11** (86 % yield).

Although the stereo- and regioselective attachment of the carbohydrate sector to compound **13** constitutes a significant achievement in this synthesis, the configurational stability of the α -*C*-glycosidic bond in α -**11** and in subsequent intermediates is a matter of much concern. You will note that the D-fucose sugar ring in α -**11** supports a concatenation of sterically hindered groupings, a circumstance that could provide the driving force for a destructive anomerization process. Indeed, the glycosidic linkage in the gilvocarcins is known to be susceptible to anomerization and/or ring-enlargement reactions under acidic conditions, presumably through the intermediacy of a quinone methide species (see **21** in Scheme 5).^{2g,3v} The production of a transient quinone methide at any stage in the synthesis would likely result in the formation of an equilibrium mixture of furanoside/pyranoside anomers. Thus, the intro-



Scheme 4. Suzuki's *O* \rightarrow *C*-glycoside rearrangement strategy.

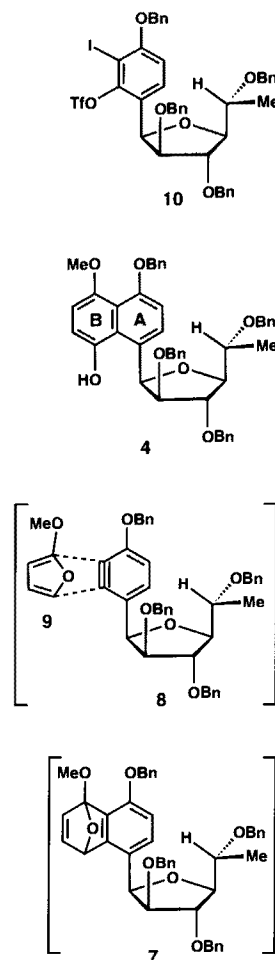


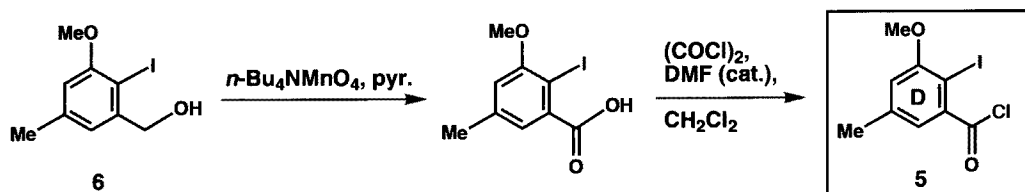
Scheme 5. Acid-induced anomerization of the gilvocarcin-type glycosidic linkage.

duction of the carbohydrate domain at such an early stage in the synthesis must be regarded as a very daring move because the acid lability of the gilvocarcin-type glycosidic linkage imposes a significant constraint on potential pathways for the synthesis of the rest of the molecule.

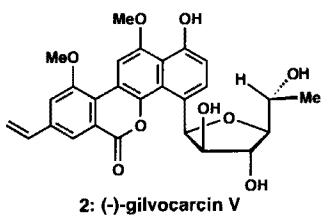
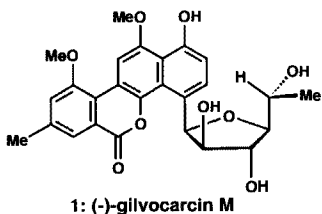
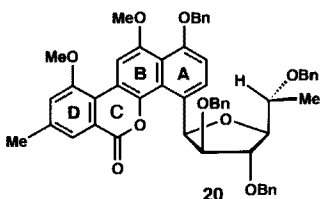
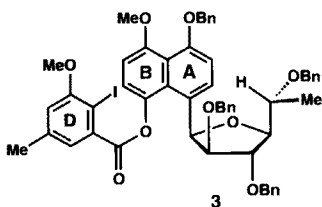
As it turns out, the elaboration of gilvocarcins M (**1**) and V (**2**) from intermediate *α*-**11** (see Scheme 3) only requires a handful of steps. Conversion of the free phenolic hydroxyl group in *α*-**11** to the corresponding triflate (**10**) can be brought about by trifluoromethanesulfonic anhydride and Hünig's base. Exposure of a cold (-78°C) solution of *ortho*-iodotriflate **10** and 2-methoxyfuran (**9**) in THF to *n*-butyllithium (2 equiv) results in the formation of naphthol **4** in 88% yield together with 7% of a regioisomeric naphthol. In this most productive transformation, *n*-butyllithium effects an iodine–lithium exchange reaction to give, after elimination of the adjacent triflate function, benzyne **8**. The latter substance is highly reactive and it participates in a facile, regioselective, intermolecular [4+2] cycloaddition reaction with 2-methoxyfuran (**9**) to give **7** as the initial adduct. Once formed, intermediate **7** suffers C–O bond cleavage and undergoes conversion to naphthol **4**. The regioselectivity displayed in the [4+2] cycloaddition step is noteworthy. It was anticipated that the benzyloxy substituent in benzyne **8** would, through an electron-withdrawing inductive effect, guide the formation of the desired head-to-head regioisomer **7**. Support for this prediction was obtained from a model study designed to assess the feasibility of the benzyne–furan cycloaddition approach to the synthesis of differentially protected naphthols.¹³

Acid chloride **5**, prepared in two straightforward steps from the known benzylic alcohol **6**^{4e} (see Scheme 6), reacts smoothly with naphthol **4** to give ester **3** in 91% yield (see Scheme 3). With an





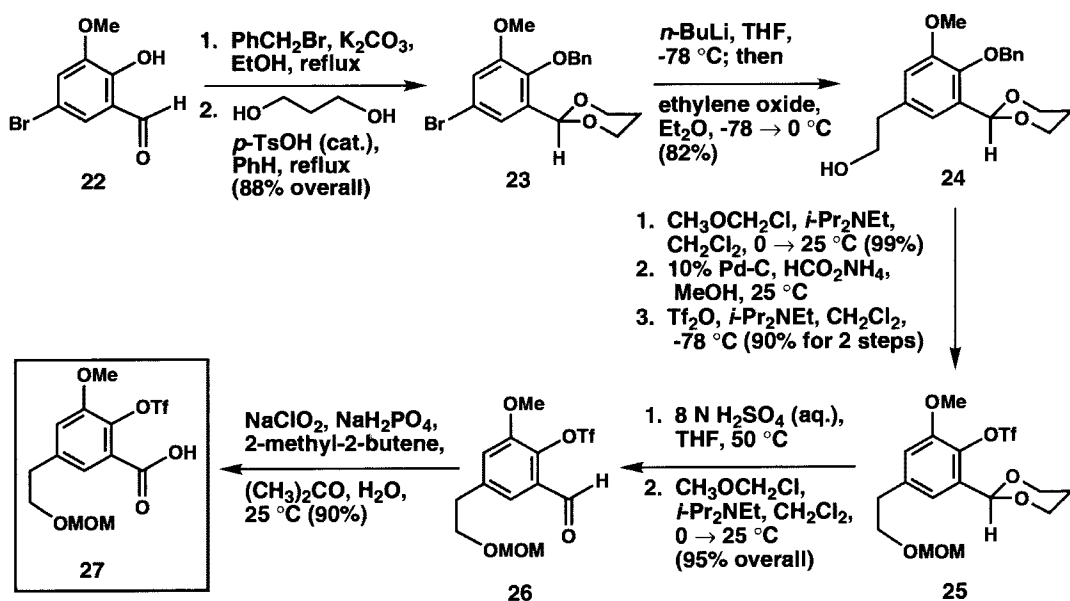
Scheme 6. Synthesis of intermediate 5.



appropriately placed iodine atom, intermediate **3** seems poised for a Pd-mediated cyclization reaction.^{4h} Indeed, treatment of **3** with bis(triphenylphosphine)palladium(II) chloride (Ph_3P)₂PdCl₂ (26 mol %) and sodium acetate (3 equiv.) in *N,N*-dimethylacetamide (DMA) at 125 °C effects the crucial intramolecular biaryl coupling and affords tetracycle **20** in 90 % yield (see Scheme 3). Finally, hydrogenolysis of the four benzyl groups furnishes (–)-gilvocarcin M (**1**) in 90 % yield. The synthetic material was found to be identical in all respects to natural gilvocarcin M.

Due, in large part, to the promising antitumor activity of gilvocarcin V (**2**), it was of interest to modify the approach outlined above so that a total synthesis of **2** could also be achieved. Not surprisingly, the gilvocarcin V synthesis exercised the same basic strategy that was so successful in the synthesis of gilvocarcin M (**1**). Compounds **1** and **2** differ only with respect to the substituent attached to C-8 of the aromatic sector; whereas gilvocarcin M (**1**) possesses a C-8 methyl group, gilvocarcin V (**2**) is distinguished by a C-8 vinyl group. Thus, the synthesis of **2** requires the elaboration of a D-ring acylating agent that carries the C-8 vinyl group either directly or in latent form.

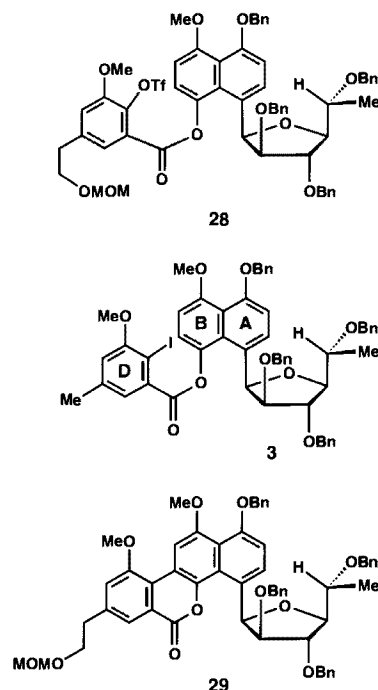
Schemes 7 and 8 detail Suzuki's synthesis of (–)-gilvocarcin V (**2**). It was decided to construct a D-ring acylating agent bearing a latent C-8 vinyl group. To this end, benzylation of the known 5-bromo-*ortho*-vanillin (**22**),¹⁴ followed by protection of the aldehyde carbonyl in the form of a cyclic acetal (1,3-dioxane), affords compound **23** in 88 % overall yield (see Scheme 7). When **23** is subjected to the action of *n*-butyllithium at –78 °C, a halogen–lithium exchange reaction takes place to give a reactive aryllithium reagent which could, in principle, be intercepted by a host of electrophiles. When ethylene oxide is used as the electrophile, alcohol **24** forms smoothly (82 %). Sequential protection and deprotection reactions afford a phenol which is subsequently converted to triflate **25** with trifluoromethanesulfonic anhydride and Hünig's base (89 % overall yield). Unfortunately, acid hydrolysis of the dioxane ring is attended by cleavage of the methoxymethyl (MOM) protecting group. It was, therefore, necessary to reprotect the primary hydroxyl. Aldehyde **26**, prepared in this manner, can be easily oxidized to the desired carboxylic acid **27** with sodium chlorite.¹⁵

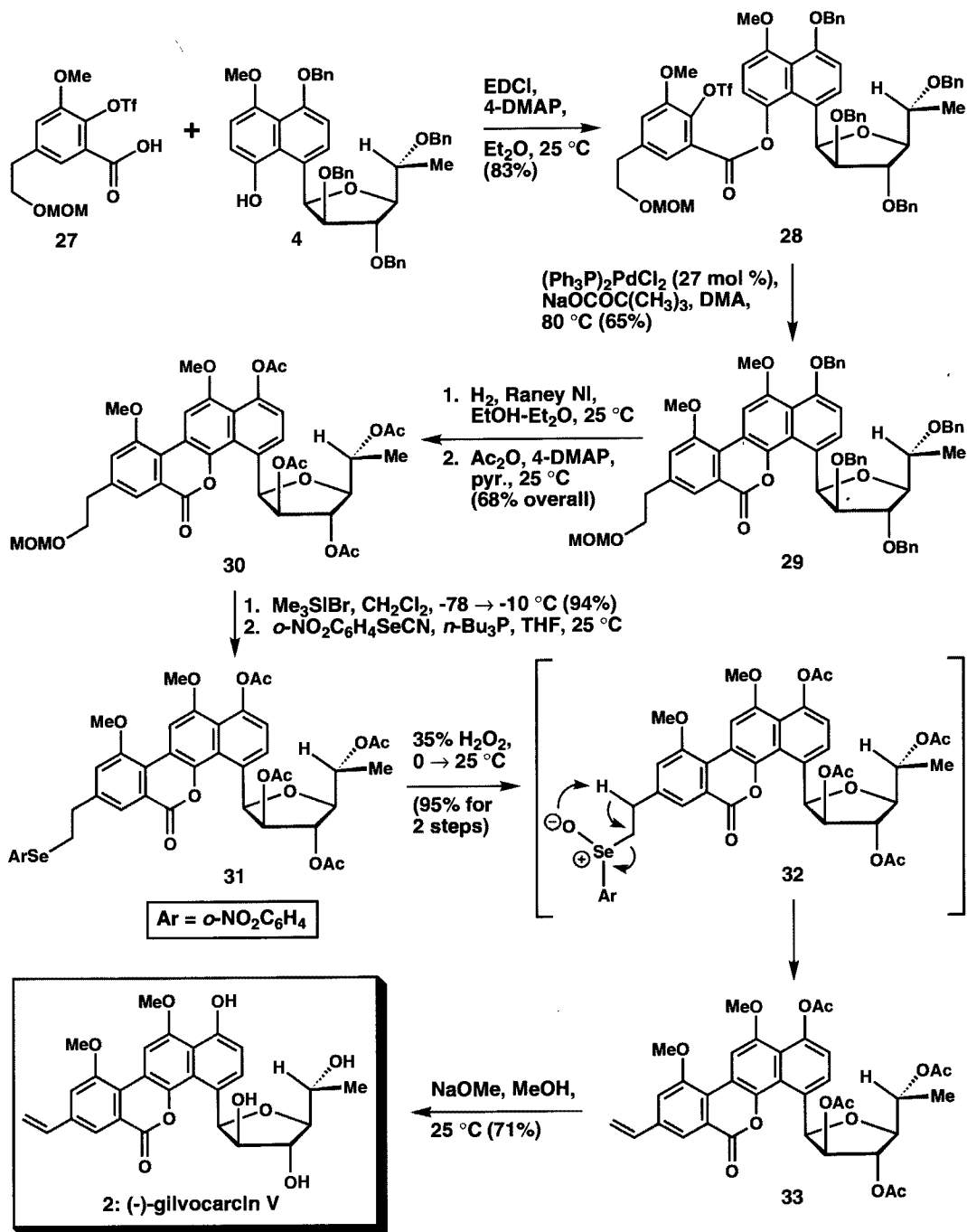


Scheme 7. Synthesis of intermediate 27.

Although intermediate **27** is not a competent acylating agent, it combines smoothly, in the desired and expected way, with naphthol **4** in the presence of the water-soluble 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDCI) and 4-dimethylaminopyridine (4-DMAP) to give ester **28** (83% yield) (see Scheme 8). The lability of the MOM ether thwarted all attempts to convert **27** into the corresponding acid chloride. The acquisition of ester **28**, with its conspicuous triflate grouping, set the stage for the internal biaryl coupling reaction. In contrast to the ease with which aryl iodide **3** can be induced to cyclize (see Scheme 3), aryl triflate **28** does not cyclize efficiently under the same reaction conditions. After a good deal of careful experimentation, it was found that the crucial biaryl coupling can be effected in acceptable yields when sodium pivalate is used in place of sodium acetate. Thus, treatment of a solution of triflate **28** in *N,N*-dimethylacetamide (DMA) with $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (27 mol %) and sodium pivalate at 80°C affords **29** in 65% yield together with 21% recovered starting material. It is noteworthy that this cyclization reaction can be effected at a temperature 45 K lower than that used in the cyclization of aryl iodide **3**.

The completion of the synthesis of gilvocarcin V (**2**) only requires a few functional group manipulations. Hydrogenolysis of the four benzyl groups, followed by acetylation of the liberated hydroxyl groups, provides **30** in 68% overall yield. After cleavage of the MOM ether in **30** with bromotrimethylsilane, application





Scheme 8. Synthesis of (-)-gilvocarcin V (2).

of Grieco's *ortho*-nitrophenylselenenylation procedure¹⁶ permits the synthesis of *ortho*-nitrophenylselenide **31**. Oxidation of the selenium atom in **31** with hydrogen peroxide produces transient selenoxide **32**, which undergoes facile elimination to alkene **33**. Finally, treatment of **33** with sodium methoxide in methanol accomplishes the cleavage of all four acetate esters and gives (–)-gilvocarcin V (**2**) in 71 % yield.

29.4 Conclusion

The syntheses of gilvocarcins M (**1**) and V (**2**) by Suzuki and co-workers rely on an exceedingly concise and elegant general strategy. Starting from readily available building blocks, Suzuki's gilvocarcin M synthesis requires only six steps! The basic strategy comprises four crucial bond constructions: aryl *C*-glycosylation, benzyne–furan [4+2] cycloaddition, convergent acylation, and Pd-induced biaryl coupling.

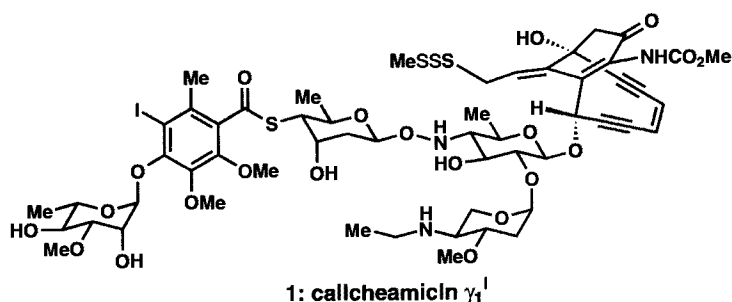
During the course of model studies,⁹ an effective solution to the nontrivial problem of constructing aryl *C*-glycosides emerged. In particular, it was found that the combined action of Cp₂HfCl₂ and AgClO₄ can induce the formation of a carbon–carbon bond between the *ortho* position of a phenol and the anomeric carbon of a carbohydrate. Interestingly, this process includes a temperature dependent *O* → *C*-glycoside rearrangement, and, in the context of the gilvocarcin synthesis, it accomplishes a contrasteric aryl *C*-glycosylation. This gilvocarcin synthesis showcases the utility of the novel Cp₂HfCl₂–AgClO₄ aryl *C*-glycosylation promoter.

The annulation of ring B through a regioselective benzyne–furan [4+2] cycloaddition reaction (see **9+10** → **4**, Scheme 3) is also noteworthy. This elegant tandem transformation¹⁷ includes three distinct reactions. Subjection of iodotriflate **10** to a halogen–lithium exchange reaction produces the highly reactive benzyne **8**, which subsequently participates in a facile and regioselective Diels–Alder reaction with 2-methoxyfuran (**9**). The intermediacy of [4+2] adduct **7** is transitory, for it suffers C–O bond cleavage *in situ* and undergoes conversion to naphthol **4**. Through its free hydroxyl group, naphthol **4** can be conveniently linked to suitably functionalized D-ring acylating agents. And then, in an exceedingly simple and striking maneuver, the crucial bond joining aromatic rings B and D can be fashioned through a Martin-type Pd-mediated cyclization reaction.^{4b} A virtue of Suzuki's convergent gilvocarcin synthesis strategy is that it seems ideally suited for the elaboration of D ring modified analogs.

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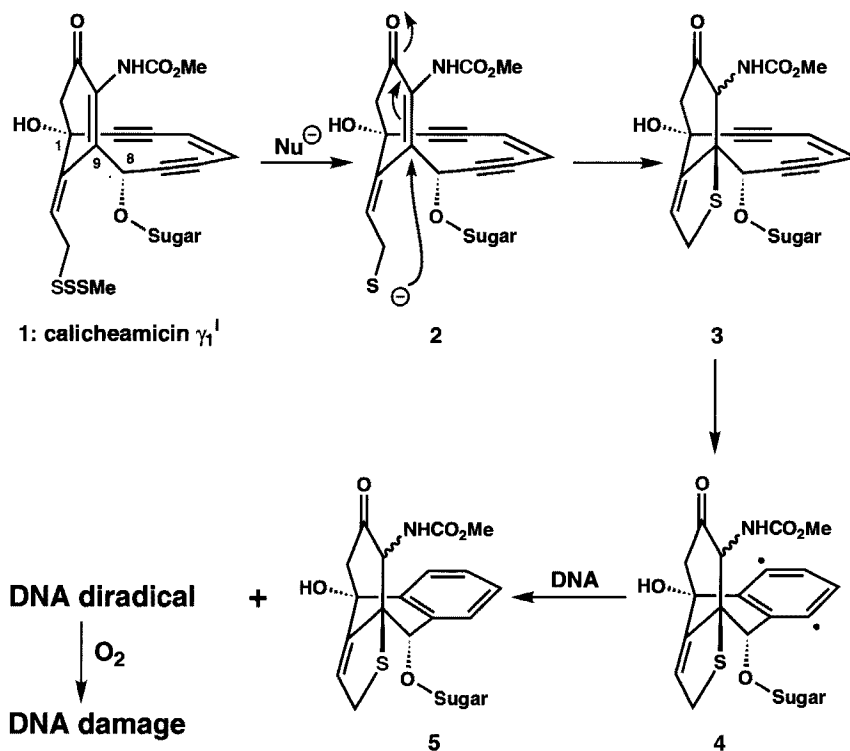


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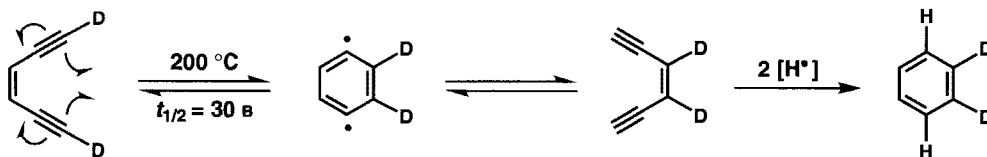
Calicheamicin γ_1^I

30.1 Introduction

The story of calicheamicin γ_1^I (**1**), the most prominent member of the enediyne class of natural products, began in the early 1980s, when a touring scientist collected chalky rocks (*caliche* in Greek) from a site near a Texas highway. Contained within these rocks were bacteria (*Micromonospora echinospora* ssp *calichensis*) which, when grown in laboratory cultures, produced calicheamicin γ_1^I (**1**) along with a series of related compounds. The phenomenally high potency of calicheamicin γ_1^I (**1**) against tumor cells provided the impetus for its structural elucidation,¹ thereby revealing the sinister weaponry used by the organism against its enemies. Calicheamicin's structure was completely unprecedented at the time of its discovery. It is composed of three main domains: (1) the enediyne segment ("molecular warhead"); (2) the trisulfide moiety ("triggering device"); and (3) the oligosaccharide chain ("recognition device" or "delivery system"). The molecular structure of calicheamicin γ_1^I (**1**) is a masterful piece of molecular design by nature. To appreciate its sophistication and beauty one has only to look at its mechanism of action (see Scheme 1) which involves: (a) activation by a nucleophilic attack upon the trisulfide triggering device; (b) intramolecular conjugate addition of the generated thiolate nucleophile to the enone functionality; and (c) a Bergman cycloaromatization reaction² to form a highly reactive 1,4-benzenoid diradical, which attacks DNA, causing lethal double-strand cuts to the genetic material and conversion of the diradical to a benzenoid system. In engineering this ingenious molecular assembly, nature made use of the Bergman reaction² (Scheme 2) and fine-tuned its reactivity by a series of clever moves and devices, including: (a) lowering the



Scheme 1. Proposed mechanism of action of calicheamicin γ_1^I (1).



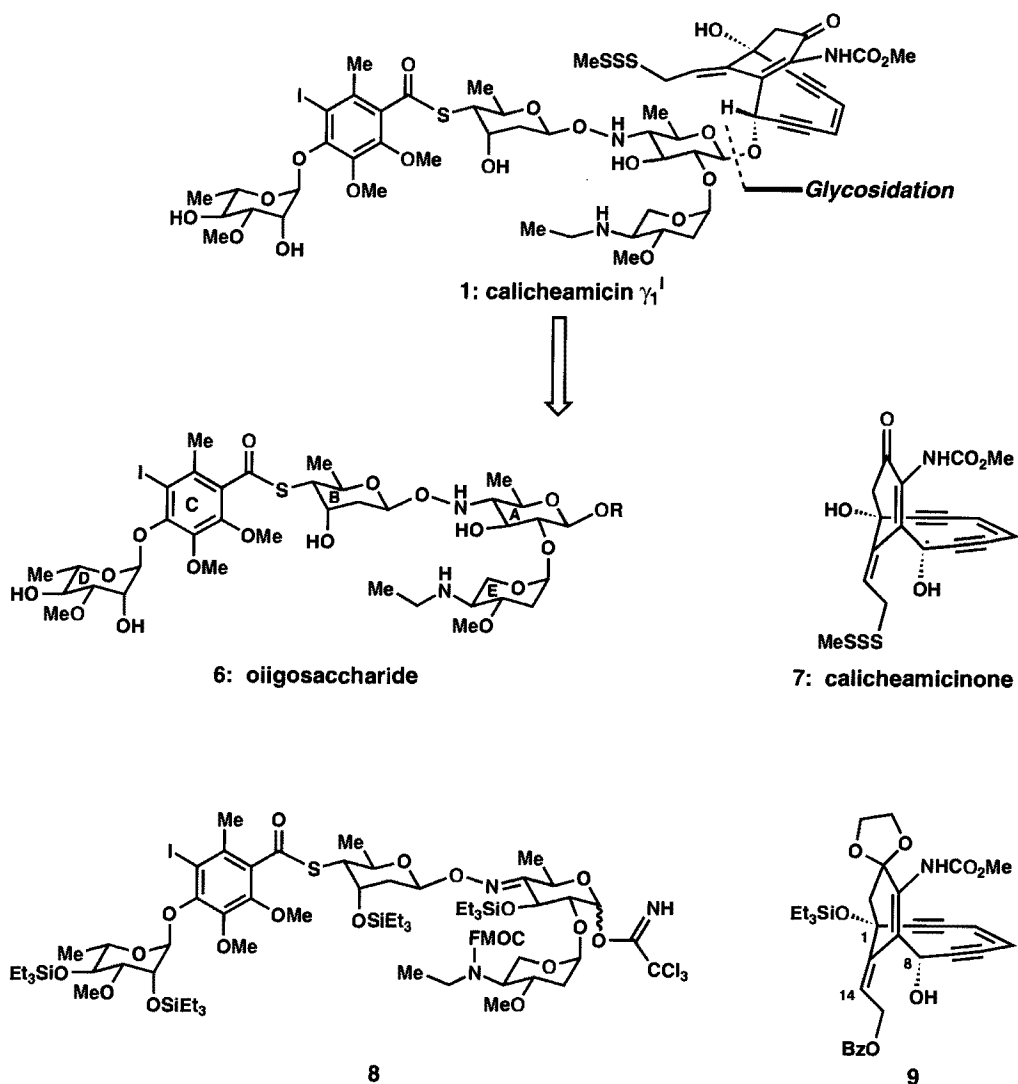
Scheme 2. The Bergman cycloaromatization reaction.

reaction's energy of activation by confining the enediyne moiety to a ten-membered ring; (b) endowing the molecule with chemical stability prior to activation by building a locking device in the form of a double bond at a strategic site (cyclohexenone) within its framework; and (c) installing in its structure an allylic double bond with the proper geometry as a carrier for the trisulfide triggering device in order to allow interaction of the generated thiolate nucleophile with the enone functionality upon activation. In addition to these strategic architectural features, calicheamicin γ_1^I (**1**) possesses a novel oligosaccharide binding domain that serves as a delivery system.³ The iodine atom on the phenyl ring may seem an unusual addition at first glance, but it plays an important role: it enhances the binding affinity of the molecule to its target, DNA.⁴ All told, calicheamicin γ_1^I (**1**) is a highly sophisticated molecule that displays extraordinary efficiency in seeking and destroying DNA, thus inducing cell death. Another remarkable feature of this molecule is its ability to selectively bind and cut specific sequences of double-stranded DNA such as TCCT, TCTC, and TTTT.⁵

As one of nature's most extraordinary non-polymeric, molecular assemblies, calicheamicin γ_1^I (**1**) offers a formidable challenge to synthetic organic chemists. Its molecular architecture combined with its important biological activity and fascinating mechanism of action provided a unique and rare opportunity for creative adventures in organic synthesis, molecular design, and biology.⁶ The highly strained ten-membered ring enediyne moiety, the trisulfide unit, the novel NH–O glycosidic bond, and the fully substituted aromatic ring are challenging features of this molecule. Even more formidable is the task of assembling these functionalities together and in the right order so as to achieve a total synthesis. Below we describe the evolution of the strategy that led to the first successful total synthesis of calicheamicin γ_1^I (**1**).⁷

30.2 Retrosynthetic Analysis and Strategy

The complex structure of calicheamicin γ_1^I is composed of two distinct domains that are revealed by retrosynthetic cleavage of the indicated glycosidic bond in **1** (see Scheme 3). The elaborate oligosaccharide domain **6** confers remarkable sequence specificity to the binding of **1** within the minor groove of double-stranded DNA, while the aglycon **7**, with its unique pattern of unsaturation and appropriately placed trisulfide triggering device, is responsible for calicheamicin's potent DNA-cleaving properties. At an early stage of the analysis, we decided to commit ourselves to the pursuit of a highly convergent strategy for the synthesis of this multifunctional and sensitive natural product. Indeed, the convergent union of suitably differentiated representatives of the oligosaccharide and aglycon sectors constitutes the cornerstone of this strategy.



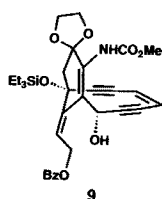
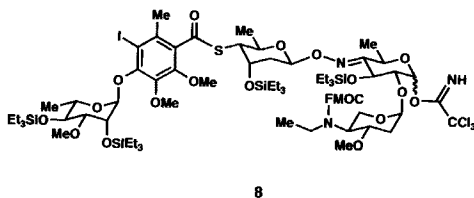
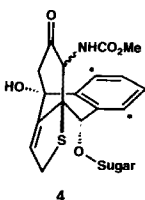
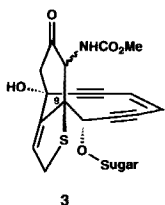
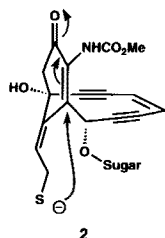
Scheme 3. Retrosynthetic analysis of calicheamicin γ_1^I (1).

Before we commence with a more complete retrosynthetic analysis of calicheamicin γ_1^I (**1**), some further comments regarding the structure of this remarkable natural product are in order. The constitution of calicheamicin's aryl tetrasaccharide substructure **6** is very unusual and intimidating. At the outset, it was surmised that the B-ring of **6** would probably present the most difficult challenge to any synthesis of the oligosaccharide sector. Pyran ring B supports two conspicuous and novel structural features. Connected to the 4-position of ring B is a hexasubstituted thiobenzoate ester, and interposed between rings A and B is an unusual and easily reduced N–O linkage. The N–O link is attached through its nitrogen atom to the 4-position of ring A, while its oxygen atom is appended to the anomeric carbon atom of ring B. A closer examination of the central B-ring reveals that the configuration of the anomeric carbon is β and that the 2- and 6-positions lack oxygen substituents. Although 2,6-dideoxy- β -glycosides are expressed in several biologically active natural products, the development of efficient methodology for the synthesis of β -linked 2-deoxy sugars has been a long-standing problem in the field of oligosaccharide synthesis.⁸

Traditionally, β -selective glycosidations have been achieved by using neighboring group active glycosyl donors. After activation of the anomeric carbon of the glycosyl donor, an appropriately placed heteroatom substituent in the 2-position guides, through anchimeric assistance, the stereochemical course of the glycosidation reaction. After the desired β -glycosidic bond has been formed stereoselectively, the superfluous C-2 heteroatom substituent can then be reductively cleaved to give a β -linked 2-deoxy sugar. Thus, through the use of a neighboring group active glycosyl donor, it ought to be possible to define the requisite β configuration of the anomeric center in ring B of intermediate **6**. However, the prospects for effecting the reductive removal of a C-2 stereocontrolling group from a molecule that already contains a relatively weak and easily reducible N–O bond did not seem favorable. In fact, early experiments demonstrated that the reductive removal of a C-2 substituent in the presence of an N–O linkage would be troublesome.

As impressive as the oligosaccharide domain is, calicheamicinone, the aglycon sector **7** (see Scheme 3) is the most striking substructure of calicheamicin γ_1^I . The rigid bicyclic framework of **7** accommodates an unusual allylic methyl trisulfide and a novel pattern of unsaturation that had not been encountered in natural products before.

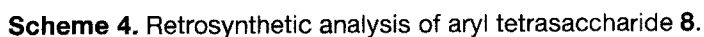
A few more comments regarding the fascinating mode of action of this remarkable molecule are in order here. With respect to calicheamicin's potent DNA-cleaving properties, the oligosaccharide domain, the *trans* allylic trisulfide, the α,β -unsaturated ketone, and the conjugated 1,5-diyn-3-ene moiety all participate in a remarkable cascade of reactions leading to the production of a highly reactive and short-lived species that is lethal to the genetic material (see Scheme 1). In the presence of double-stranded DNA, the oligosaccharide domain of the intact natural product anchors the molecule



within the minor groove, after which the allylic trisulfide residue undergoes reduction to give an allylic thiolate ion (see intermediate **2**, Scheme 1). By virtue of the *trans* carbon–carbon double bond geometry, this newly formed nucleophilic thiolate finds itself in proximity to the electrophilic β carbon atom of the cyclohexenone. In such a favorable setting, a facile intramolecular Michael addition reaction takes place to give **3** as a transient intermediate. Evidently, the conformational change which attends the C-9 $sp^2 \rightarrow C-9$ sp^3 hybridization change is sufficient to induce Bergman cycloaromatization² of the enediyne system, generating the highly reactive benzenoid diradical **4**; it is this aggressive diradical that initiates cleavage of duplex DNA by abstracting hydrogen atoms from the phosphate sugar backbone. With respect to the trisulfide cleavage step, Myers *et al.* demonstrated, in an elegant series of experiments,⁹ that reduction of the trisulfide moiety can occur by an attack of glutathione, the putative nucleophile in this process, upon either one of the three sulfur atoms in **1**. Nevertheless, each of the discrete trisulfide cleavage products ultimately converge upon the same dihydrothiophene intermediate **3** via different reaction paths and at different rates.

Although our group had previously described syntheses of both domains of calicheamicin $\gamma_1^{1,7a,b,d,e}$ each in its naturally occurring stereochemical form, projections regarding the compatibility of the numerous functional groups in **1** with the final stages of the synthesis led to the definition of intermediates **8** and **9** as suitable surrogates for the oligosaccharide and aglycon sectors of the natural product, respectively (Scheme 3). It was hoped that the Schmidt trichloroacetimidate glycosidation protocol^{8d,10} could accomplish the union of intermediates **8** and **9** through a glycosidic bond. The Fmoc and triethylsilyl protecting groups were selected for use in this synthesis because they represent the best balance between stability and ease of removal. Schemes 4 and 5 present detailed retrosynthetic analyses of key intermediates **8** and **9**, respectively.

A conspicuous structural feature of key intermediate **8** is the oxime ether function (see Scheme 4). It was anticipated that this group could serve as a stable precursor for the labile NH–O linkage; in the synthetic direction, a stereoselective reduction of the C–N π bond, preferably at a late stage in the synthesis, could complete the introduction of the unstable NH–O moiety. By virtue of its multifunctional nature, intermediate **8** presents several convenient opportunities for molecular simplification. Nevertheless, the option afforded by retrosynthetic cleavage of the indicated bonds appeared particularly attractive. In the forward sense, acylation of the free thiol function in **11** with acid chloride **10**, followed by a short sequence of functional group manipulations, was expected to furnish intermediate **8**. Compound **10** comprises rings C and D of the targeted oligosaccharide sector, and it can be traced to intermediates **12** and **13** by cleavage of the α -glycosidic bond. On the basis of the well-documented success of the Schmidt trichloroacetimidate glycosidation method,^{8d,e} it was anticipated that upon



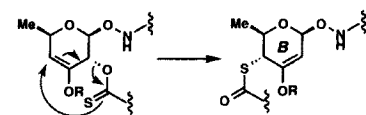
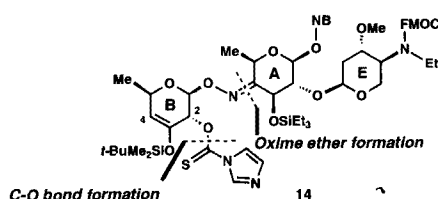
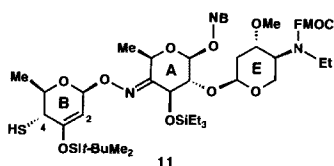
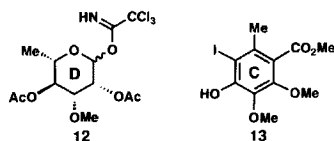
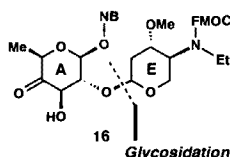
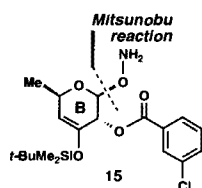


Figure 1. Stereospecific [3,3]-Sigmatropic rearrangement strategy for the construction of ring B. R = Sit-BuMe₂.



activation of the anomeric position in **12** with a Lewis acid such as $\text{BF}_3 \cdot \text{OEt}_2$, the C-2 acetoxy function would guide the stereochemical course of a glycosidation reaction employing hexasubstituted phenol **13** as the glycosyl acceptor. Through anchimeric assistance,¹¹ the axially disposed C-2 acetoxy function in **12** was expected to guide the formation of the requisite α -glycosidic bond (see intermediate **49**, Scheme 8). A short sequence of functional group manipulations could then secure the formation of key intermediate **10**.

In marked contrast to the seemingly straightforward manner in which the C–D substructure could potentially be constructed, trisaccharide **11** presents a more formidable challenge to synthesis. It is during the course of the synthesis of **11** that we would have to contend with the B-ring problem. In particular, some method would have to be developed that would permit the formation of the B-ring β -glycosidic linkage. In addition, a strategy for the incorporation of the sulfur atom at C-4 would have to be devised. With respect to the former objective, we were cognizant of the difficulty inherent in any approach based on the reductive cleavage of a C-2 stereocontrolling heteroatom function in the presence of a reducible N–O linkage. As matters transpired, our predictions regarding the recalcitrance of the B-ring pyran were justified. Nevertheless, a great deal of persistent experimentation and a careful analysis of the problem led to the formulation of the straightforward and efficient strategy depicted in Scheme 4. It was hoped that intermediate **14** could be induced to participate in a [3,3] sigmatropic rearrangement to give the isomeric S-bound imidazoethiocarboxylate (see Fig. 1 and **14** \rightarrow **69** \rightarrow **70**, Scheme 14). Sulfide **11** could then be formed after a simple sulfur deprotection step. This allylic transposition strategy appeared particularly attractive because it could simultaneously accomplish the necessary deoxygenation of the 2-position in ring B and the stereospecific introduction of the requisite sulfur atom at the 4-position. With an oxygen atom at the 2-position of ring B in **14**, it might also be possible to establish, at some stage, the requisite β configuration at the adjacent anomeric center through neighboring group participation. Incidentally, during the course of our synthetic studies, the *ortho*-nitrobenzyl function (NB) presented itself as a useful protecting group for the A-ring anomeric hydroxyl; this protecting group is stable under a wide range of reaction conditions and yet it can be removed photolytically under mild conditions.

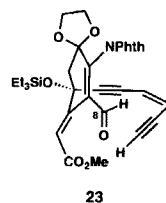
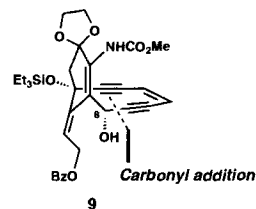
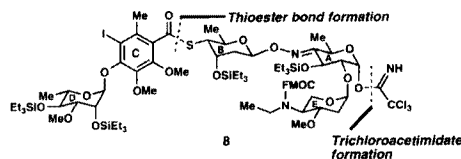
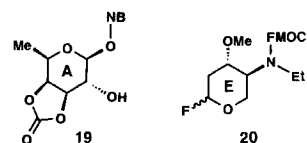
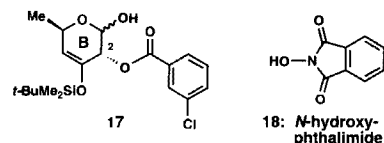
Compound **14** can be dismantled in a productive fashion by retrosynthetic cleavage of the indicated bonds (see Scheme 4). The intermolecular attack of the amino group in **15** upon the keto function in **16** would be expected to result in the formation of the desired oxime ether after loss of a water molecule. A few functional group manipulations would then complete the synthesis of intermediate **14**. A valuable structural feature of **15** is the C-2 oxygen substituent. Although this oxygen atom is not expressed in the natural product, it would certainly play an important role in our

approach to the synthesis of the oligosaccharide sector. In particular, the oxygen atom affixed to C-2 in **15** is part of a benzoate ester, a function known to strongly influence the stereochemical course of glycosidation reactions.^{8d-f} Thus, on the basis of substantial precedent, it was anticipated that intermediates **17** and **18** could be stereoselectively joined through a glycosidic bond. Much confidence was invested in the proposition that the appropriately placed C-2 benzoate ester function in **17** would guide the formation of the desired β -glycosidic bond upon activation of the anomeric position. After the C-2 benzoate ester has served its purpose as a stereocontrolling group for the construction of the β -glycosidic linkage of ring B, it was our plan to induce, via intermediate **14**, a 1,3-transfer of asymmetry from the 2- to the 4-position. As we have already stated, this productive [3,3] sigmatropic process could simultaneously accomplish the necessary deoxygenation at C-2 and the stereospecific introduction of a sulfur substituent at C-4.

To complete the retrosynthetic analysis of aryl tetrasaccharide **8**, the synthetic challenge posed by disaccharide ketone **16** needs to be addressed. Of course, the glycosidic bond linking the two functionalized pyran rings in **16** provides a logical site for retrosynthetic disassembly. This maneuver unveils glycosyl acceptor **19** and glycosyl donor **20** as potential precursors. An analysis of the stereochemical pattern of **19** immediately suggested the use of D-fucose (**21**) as a starting material, while **20** could potentially be derived from the methyl ester of L-serine (**22**) (Scheme 4).

It is instructive to reiterate that our strategy for the total synthesis of calicheamicin γ_1^1 (**1**) is based on the convergent union of suitably differentiated representatives of the oligosaccharide and aglycon domains of the natural product. It was projected that aryl tetrasaccharide **8**, equipped with an A-ring anomeric trichloroacetimidate function, could serve as the glycosyl donor in a Schmidt coupling reaction with the free secondary hydroxyl group of intermediate **9**; it was hoped that the glycosidating potential of **8** could be unveiled upon treatment with a Lewis acid, and that, in the presence of **9**, the crucial β -glycosidic bond joining the C-8 oxygen in **9** with the A-ring anomeric carbon in **8** would form smoothly. As attractive as this convergent approach seemed, the development of an efficient strategy for the synthesis of aglycon **9** was far from straightforward. From the beginning, all efforts were devoted to the development of an aglycon synthesis strategy that was both diastereo- and enantioselective. In the event that **9** could be prepared in enantiomerically pure form, then the subsequent coupling reaction with **8**, a substance that is of course enantiomerically pure, would furnish, at most, only two diastereomeric glycosides. Scheme 5 outlines, in retrosynthetic form, the general features of our enantioselective route to key intermediate **9**.

Retrosynthetic cleavage of the indicated bond in **9** provides acetylenic aldehyde **23** as a potential precursor. It was anticipated that the action of a suitable base on **23** would result in the formation of an acetylide anion, a competent carbon nucleophile that could





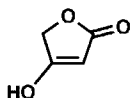
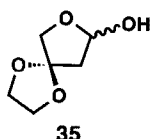
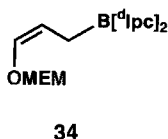
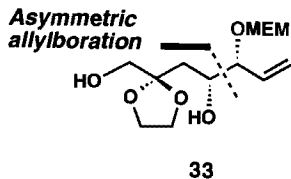
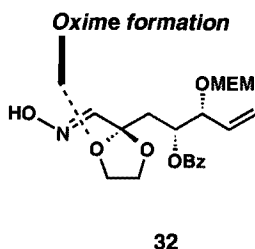
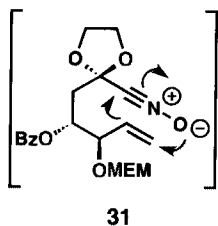
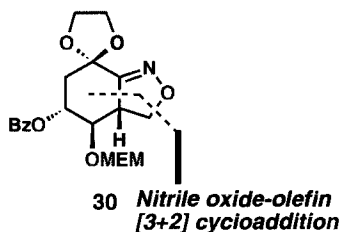
Scheme 5. Retrosynthetic analysis of aglycon **9**.

effect ring closure by an intramolecular attack on the C-8 aldehyde carbonyl.

The protected β -amino- α,β -unsaturated aldehyde is a distinguishing structural feature of **23**. Our approach to the synthesis of the calicheamicin aglycon is based on the recognition that the 1,5-relationship between the phthalimide-protected nitrogen atom and the aldehyde carbonyl oxygen could conceivably evolve from an isoxazole precursor (see intermediate **24**). The task of achieving the conversion of isoxazole **24** to **23** would require reduction of the relatively weak N–O bond, tautomerization, protection of the nitrogen atom, and deprotection of the terminal acetylene carbon. Retrosynthetic disassembly of **24** in the indicated way provides intermediates **25** and **26** as potential building blocks. This retrosynthetic maneuver appeared particularly attractive owing to the facility with which the conjugated 1,5-diyn-3-ene substructure can be assembled by a Pd-catalyzed coupling reaction.^{12–14} This reaction is well suited for the construction of a bond between sp - and sp^2 -hybridized carbon atoms, and has proven to be particularly valuable in the enediyne field.

Through an intermolecular Wittig reaction and a short sequence of protecting group manipulations, intermediate **25** could potentially be derived from keto isoxazole **27**. It seemed reasonable to expect that the fully substituted and hindered tetrahedral carbon atom adjacent to the ketone carbonyl in **27** would enforce the formation of the desired geometrical isomer in the Wittig reaction. Although the susceptibility of isoxazole rings to reduction was a matter of some concern, it was anticipated that the reagents and conditions that could bring about the conversion of **27** to **24** would not compromise the isoxazole ring in these systems. It was hoped that the reactive β -amino- α,β -unsaturated aldehyde (**23**) that would eventually be needed for the crucial ring closure reaction could be concealed in the form of an isoxazole ring.

You will note that intermediate **27** possesses a single, fully substituted stereogenic center at C-1 (calicheamicin numbering). To achieve an enantioselective synthesis of key intermediate **9**, a strategy would have to be devised that would permit the enantioselective formation of this stereocenter. Although this problem could conceivably be mastered in several different ways, it was projected that the intermolecular attack of an acetylide ion on the keto function in **29** would furnish intermediate **28** with acceptable diastereoselectivity. In this reaction, a preexisting stereocenter at C-13 (calicheamicin numbering) in **29** is used to direct the addition of trimethylsilyl acetylide to the more accessible diastereoface of the C-1 ketone. Cleavage of the methoxyethoxymethyl (MEM) protecting group in **28**, followed by oxidation of the resultant secondary alcohol, could then furnish **27**. Incidentally, the isoxazoline ring in **28** can be converted into an isoxazole by oxidation. The transfer of chirality from C-13 to C-1 in this sequence (**29** \rightarrow **28** \rightarrow **27**) is worth noting.



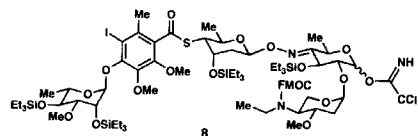
Through some conventional functional group manipulations, **29** could be elaborated from compound **30**. With three contiguous stereocenters included within a bicyclic frame, intermediate **30** poses a significant synthetic challenge. The isoxazoline ring in **30** is a conspicuous structural feature that can be regarded as the retron for the intramolecular nitrile oxide-olefin [3+2] cycloaddition transform.¹⁵ Thus, retrosynthetic disassembly of the isoxazoline ring in **30** in the manner illustrated provides **31** as a potential, albeit transient, precursor. On the basis of much precedent,¹⁶ it was projected that oxidation of the oxime function in **32** with bleach (NaOCl) would result in the formation of isoxazoline **30** through the intermediacy of nitrile oxide **31**. Although this productive transformation could potentially furnish a diastereomeric mixture of isoxazolines, both epimers could, in theory, be used in this synthesis because the new stereogenic center created in the [3+2] cycloaddition reaction is ultimately destroyed upon oxidation of the isoxazoline ring to the isoxazole (see **28** → **27**).

The synthetic problem has now been significantly simplified; an evaluation of the strategy outlined above only requires the identification of an enantioselective route for the synthesis of aldoxime **32**. The oxime function in **32** could be fashioned in a straightforward manner from the corresponding aldehyde which, in turn, could be derived from **33**. With two contiguous oxygenated stereocenters, compound **33** could conceivably be formed in one step through a diastereo- and enantioselective coupling of intermediates **34** and **35** through application of Brown's allylboration technology.¹⁷ It is important to recognize that lactol **35**, the projected electrophile in this reaction, is a participant in a ring-chain tautomeric equilibrium¹⁸ with the open hydroxy aldehyde form. Although this tautomeric equilibrium would likely be shifted substantially in favor of the closed lactol form **35**, the open-chain hydroxy aldehyde tautomer is quite electrophilic and can be intercepted by **34**. Thus, by stressing the equilibrium that exists between lactol **35** and the tautomeric hydroxy aldehyde in this manner, it ought to be possible to bring about a smooth union of intermediates **34** and **35** to give **33**. The relationship between compound **35** and commercially available tetronic acid (**36**) is obvious. In the synthetic direction, subjection of **36** to sequential protection and lactone reduction reactions could provide a simple route to lactol **35**. In the sections which follow, the reaction sequences which culminated in the first total synthesis of calicheamicin γ_1^I (**1**) are presented.

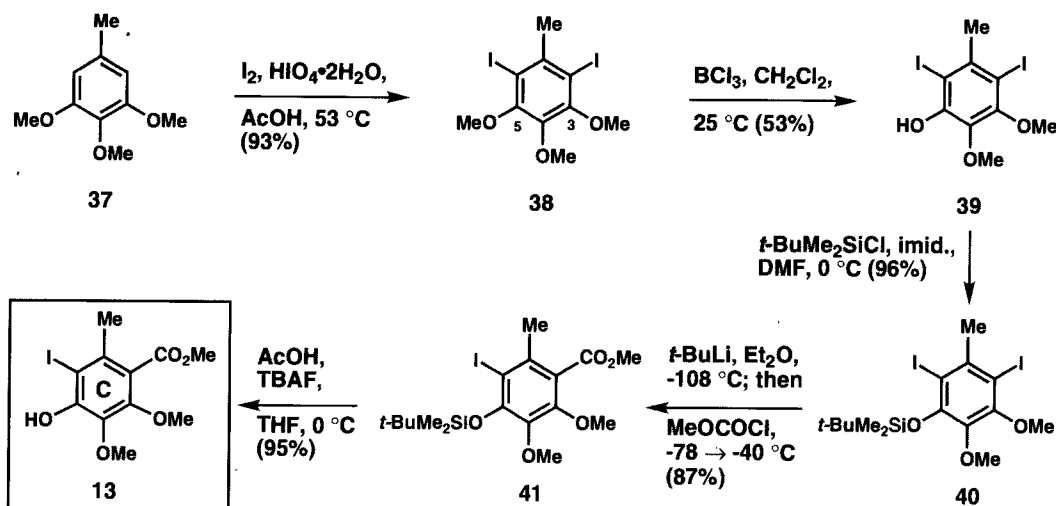
30.3 Total Synthesis

30.3.1 Synthesis of Oligosaccharide 8

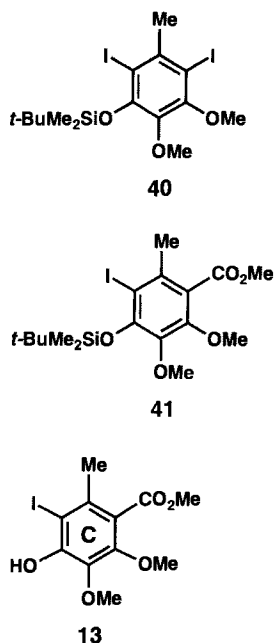
One of the more unusual structural features of calicheamicin's oligosaccharide domain is the hexasubstituted aromatic C-ring. This highly functionalized substructure is attached, through a carbonyl bridge, to the C-4 sulfur atom of ring B; and one of its oxygen atoms is joined, through an α -glycosidic bond, to a monosaccharide derived from L-rhamnose. The degree of difficulty associated with the synthesis of an aromatic nucleus that accommodates six contiguous substituents can be significant. Nonetheless, calicheamicin's hexasubstituted aromatic nucleus conceals a subtle element of symmetry, and this recognition led to the development of a concise synthetic route. Scheme 6 illustrates the synthesis of the hexasubstituted aromatic C-ring intermediate **13**.



Treatment of commercially available and symmetrical 3,4,5-trimethoxytoluene (**37**) with iodine, periodic acid, and acetic acid under the conditions of Suzuki¹⁹ results in the formation of symmetrical diiodide **38** in 93% yield. Although only one of these newly introduced iodine atoms is present in intermediate **13**, both play an important role in this synthesis. Selective monodemethylation of **38** with boron trichloride furnishes phenol **39** in 53% yield together with 13% of a regioisomer. Evidently, one of the Lewis-basic iodine substituents coordinates with the Lewis-acidic boron trichloride and directs the cleavage of the adjacent methyl ether

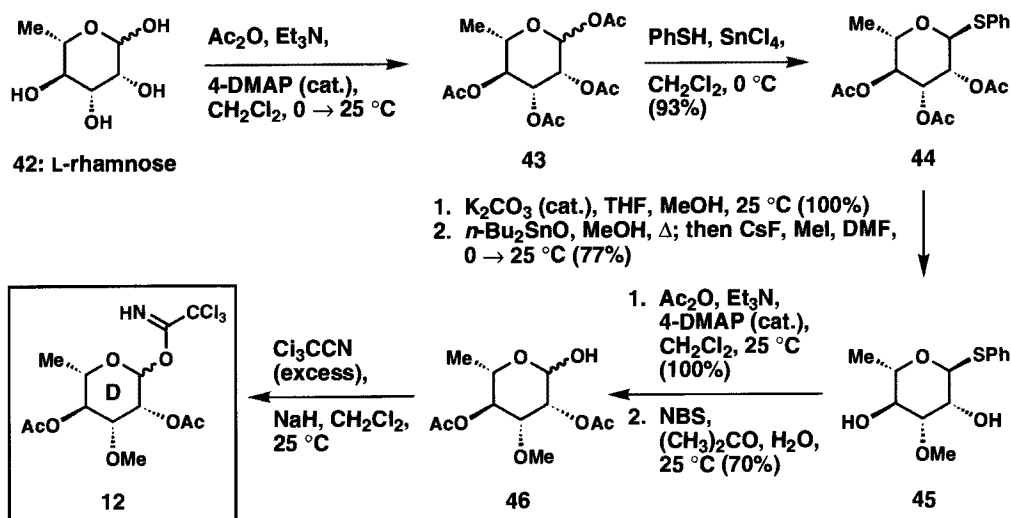


Scheme 6. Construction of oligosaccharide **8**: synthesis of intermediate **13**.



(i.e. at C-3 or at C-5) to give the desired regioisomer as the major product. In the absence of the iodine atoms, the C-4 methyl ether is cleaved preferentially. Protection of the liberated phenolic hydroxyl group as a *tert*-butyldimethylsilyl (TBS) ether with TBS chloride proceeds smoothly (96% yield) and sets the stage for a regioselective halogen-metal exchange reaction. Indeed, subsection of TBS ether **40** to the action of *tert*-butyllithium, followed by acylation of the resultant C-2 aryllithium reagent with methyl chloroformate, regioselectively furnishes methyl ester **41** in 87% yield. Finally, cleavage of the TBS ether with tetra-*n*-butylammonium fluoride (TBAF) and acetic acid completes the synthesis of C-ring intermediate **13**.

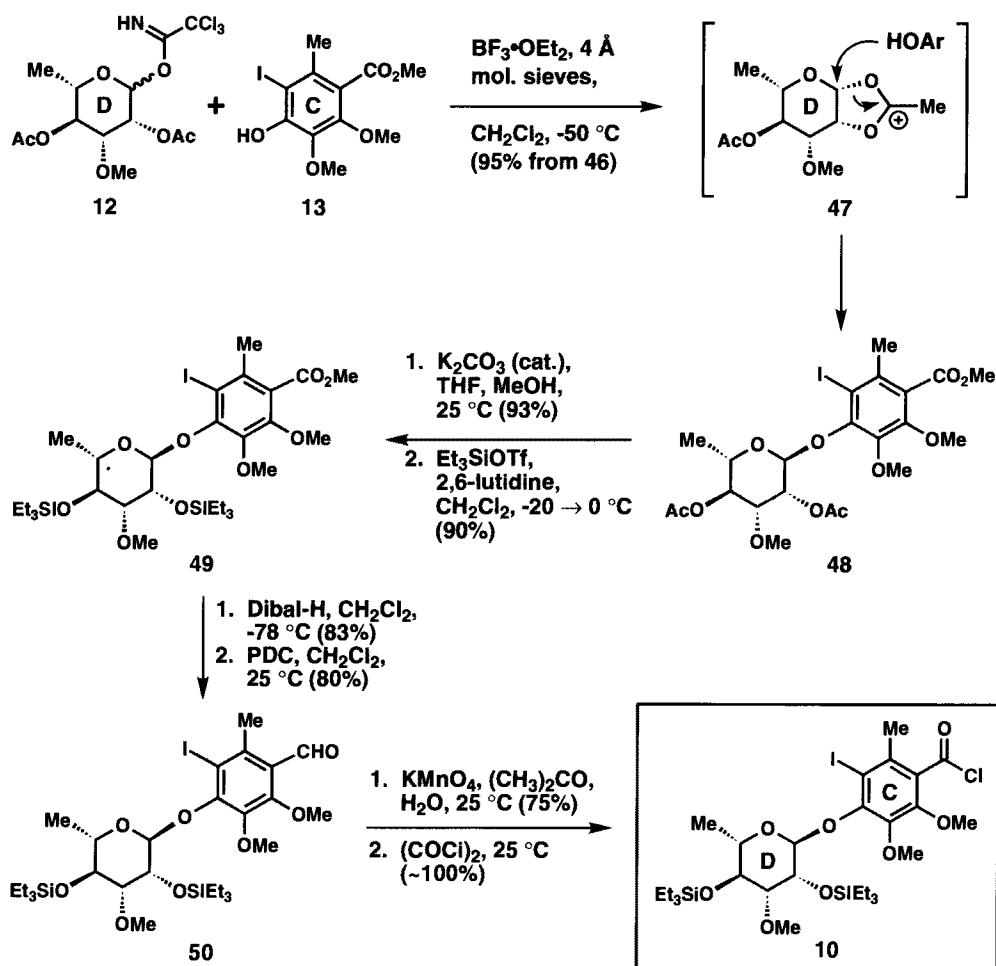
The synthesis of D-ring intermediate **12** logically employs L-rhamnose (**42**) as a starting material (see Scheme 7). Peracetylation of **42** followed by treatment of tetraacetate **43** with thiophenol in the presence of stannic chloride (SnCl_4) furnishes α -thiophenyl glycoside **44** as a single anomer in 93% yield. Addition of a catalytic quantity of potassium carbonate to a solution of **44** in methanol and THF induces solvolysis of the acetate groups and furnishes a triol which undergoes smooth and regioselective methylation on treatment with *n*- $\text{Bu}_2\text{SnO}/\text{CsF}/\text{MeI}$.²⁰ This two-step reaction sequence conveniently furnishes diol **45** in an overall yield of 77%. Quantitative bisacetylation of **45**, followed by oxidative hydrolysis of the thiophenyl glycoside with *N*-bromosuccinimide in aqueous acetone provides intermediate **46** as a mixture of α - and β -anomers. Activation of the anomeric position in **46** in the form of



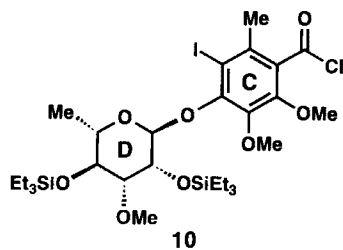
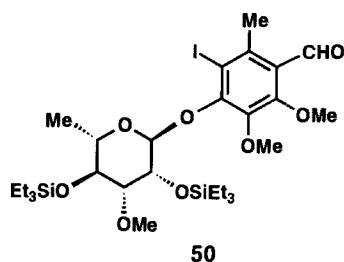
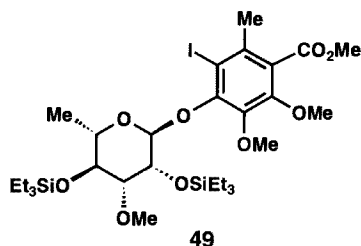
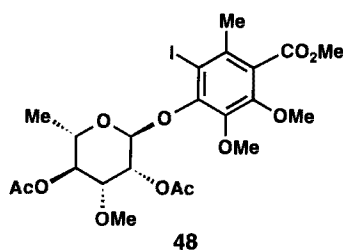
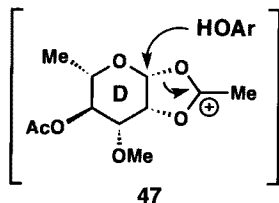
Scheme 7. Construction of oligosaccharide **8**: synthesis of intermediate **12**.

a trichloroacetimidate is easily achieved by using Schmidt's procedure.^{8d,10} In the event, the combined action of sodium hydride and excess trichloroacetonitrile on **46** in CH_2Cl_2 results in the formation of D-ring intermediate **12** in high yield, and sets the stage for an important glycosidation reaction.

It was projected that compound **13** could be stereoselectively linked, through its free phenolic hydroxyl group, with the anomeric carbon of intermediate **12** under suitably acidic conditions (see Scheme 8). Gratifyingly, the action of boron trifluoride etherate on a mixture of **12** and **13** in CH_2Cl_2 at -50°C induces a completely stereoselective glycosidation reaction, providing the desired α -anomer **48** in an excellent yield of 95% from **46**. It is presumed that boron trifluoride initiates cleavage of the anomeric trichloroacetimi-



Scheme 8. Construction of oligosaccharide **8**: synthesis of intermediate **10**.

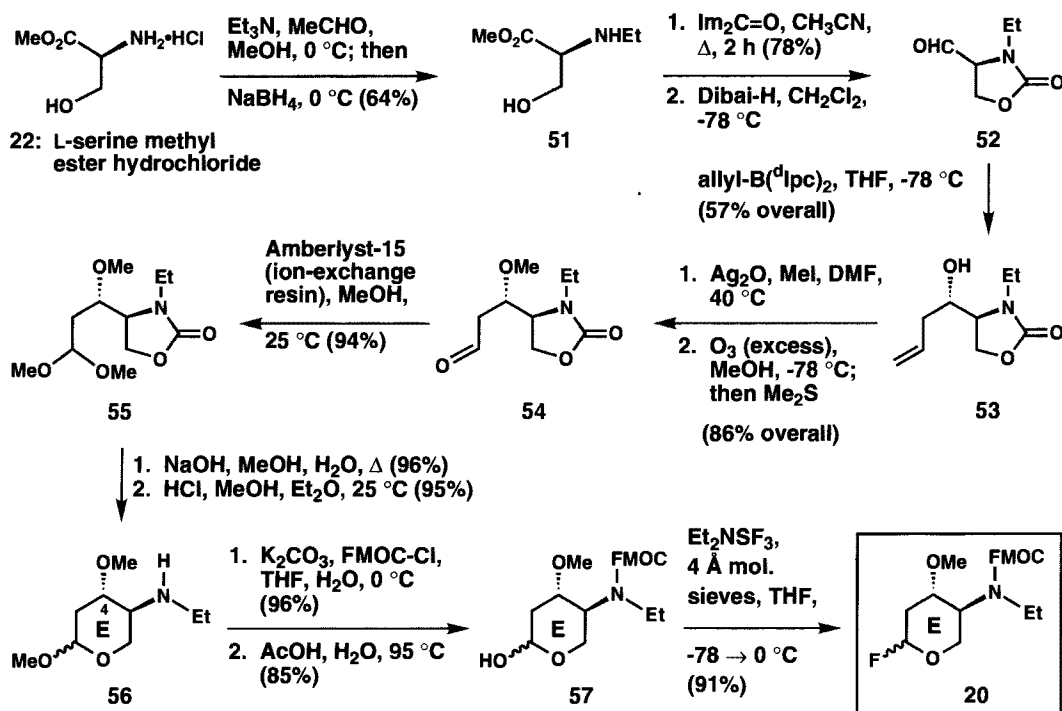


date function in **12** to give the transient acetoxonium ion **47**, which subsequently reacts with phenol **13** in a stereoselective fashion. It is important to note that the configuration of the anomeric carbon in **12** is immaterial to the stereochemical course of the glycosidation step; both anomers of **12** couple stereoselectively with **13** to give α -glycoside **48**.

At this point in the synthesis, it is necessary to exchange hydroxyl protecting groups for protecting groups compatible with subsequent stages of the synthesis. Thus, solvolysis of the acetate groups in **48**, followed by exposure of the resultant diol to triethylsilyl triflate provides intermediate **49**. The completion of the CD-ring system only requires a few functional group manipulations. Although the methoxycarbonyl function in **49** is resistant to hydrolysis, the carboxylic acid can be obtained by reduction of **49** with diisobutylaluminum hydride (Dibal-H) to the corresponding primary alcohol, followed sequentially by oxidation with pyridinium dichromate (PDC) to **50** and thence with potassium permanganate (KMnO_4). Finally, treatment of the newly formed carboxylic acid with oxalyl chloride results in the formation of acid chloride **10**, the requisite CD substructure of the oligosaccharide domain.

The synthesis of the E-ring intermediate **20** commences with the methyl ester of enantiomerically pure L-serine hydrochloride (**22**) (see Scheme 9). The primary amino group of **22** can be alkylated in a straightforward manner by treatment with acetaldehyde, followed by reduction of the intermediate imine with sodium borohydride (see **22** \rightarrow **51**). The primary hydroxyl and secondary amino groups in **51** are affixed to adjacent carbon atoms. By virtue of this close spatial relationship, it seemed reasonable to expect that the simultaneous protection of these two functions in the form of an oxazolidinone ring could be achieved. Indeed, treatment of **51** with 1,1'-carbonyldiimidazole in refluxing acetonitrile, followed by partial reduction of the methoxycarbonyl function with one equivalent of Dibal-H provides oxazolidinone aldehyde **52**.

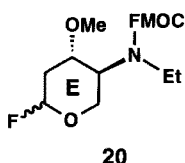
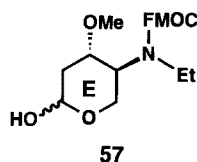
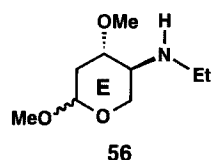
With a heteroatom-bearing stereogenic center in the α -position, aldehyde **52** might be expected to react with carbon nucleophiles in a diastereoselective manner. Although achiral organic nucleophiles will add to the aldehyde carbonyl of **52**, they do not discriminate between the two diastereotopic faces of the carbonyl. On the other hand, Brown's diisopinocampheylallyl borane, allyl-B(^dIpc) $_2$,^{17b} a useful asymmetric allylating reagent, reacts in a completely diastereoselective fashion with **52** to give allylic alcohol **53** after hydrolysis of the intermediate alkoxy borane using Evans' buffered hydroperoxide/methanol protocol.²¹ Methylation of the newly formed secondary hydroxyl group with silver oxide and methyl iodide, followed by exposure of the resultant unsaturated ether to the action of ozone, results in the formation of aldehyde **54** (86% overall yield). Although this compound is rather labile, it undergoes ready conversion to the stable dimethyl acetal **55** upon treatment with Amberlyst resin in methanol.



Scheme 9. Construction of oligosaccharide **8**: synthesis of intermediate **20**.

With the aldehyde carbonyl in suitably protected form, the oxazolidinone ring in **55**, which had served so well as a protecting group for the contiguous amino and hydroxyl functions, can be cleaved hydrolytically with sodium hydroxide under vigorous conditions (96% yield). Exposure of a solution of the newly formed amino alcohol in methanol–ether to one equivalent of HCl results in the formation of stereoisomeric lactol methyl ethers **56** (95%). Fortunately, both diastereomers can be obtained in pure form, thereby allowing verification of the configuration of the stereocenter formed during the allylboration reaction by ^1H NMR spectroscopy. The observation of large coupling constants between the axial protons on the pyran ring of the β -anomer indicates that the ring substituents are all equatorially disposed, proving that the allylboration reaction had, as predicted, created the desired configuration at the 4-position.

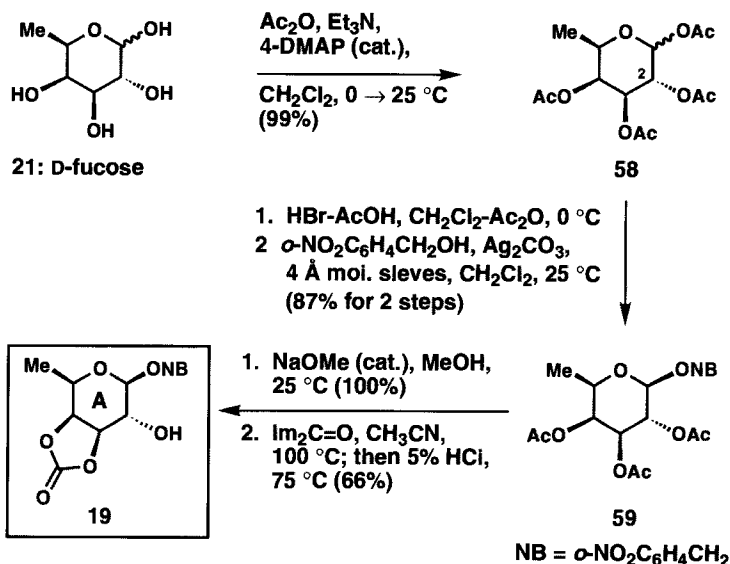
At this stage of the synthesis, it was convenient to protect the secondary amino function in **56** as the base-labile Fmoc derivative²² through the use of the corresponding chloroformate (96% yield). In the planning phase, the selection of an Fmoc protecting



group for the E-ring amino function seemed ideal. Although it was potentially too labile, this concern was outweighed by the need for a protecting group that could be easily removed in the final stages of the synthesis. While the use of the FMOC protecting group proved to be a good choice, it had the drawback that slow rotation about the C–N bond afforded a mixture of rotational isomers and complicated the NMR spectra; the best spectra were obtained in $[D_6]DMSO$ at temperatures of about 340 K.

After protection of the secondary amino group in intermediate **56**, the acid-labile lactol methyl ether function is hydrolyzed at 95 °C with aqueous acetic acid, producing **57** as a mixture of lactol diastereomers in 85 % yield. It is instructive to reiterate that the E-ring building block is to serve as a glycosyl donor in a glycosylation reaction with a suitably differentiated A-ring intermediate (see Scheme 4). Lactol **57** can therefore be regarded as a versatile synthetic intermediate; by virtue of its free anomeric hydroxyl group, **57** could serve as a common precursor for several active glycosylating agents. Thus, if necessary, a number of glycosylation protocols could be evaluated. One particularly attractive option is afforded when lactol **57** is treated with diethylaminosulfur trifluoride ($Et_2NSF_3 \equiv DAST$)²³ (see Scheme 9). This efficient reaction provides glycosyl fluoride **20**, a suitably activated E-ring glycosyl donor in high yield (91 %).

Scheme 10 details the synthesis of A-ring glycosyl acceptor **19**. The stereochemical relationship of **19** to D-fucose (**21**) is obvious. Peracetylation of D-fucose provides tetraacetate **58** in nearly quanti-

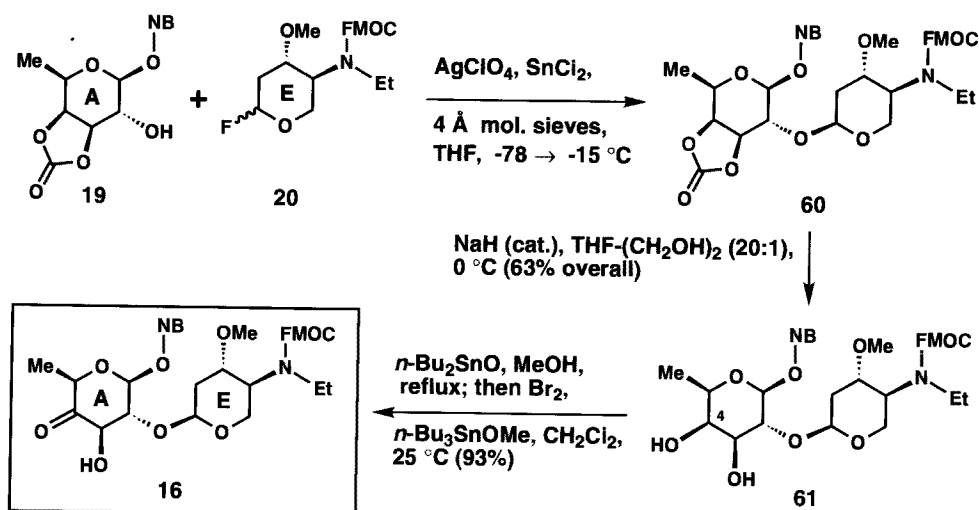


Scheme 10. Construction of oligosaccharide **8**: synthesis of intermediate **19**.

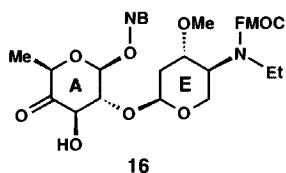
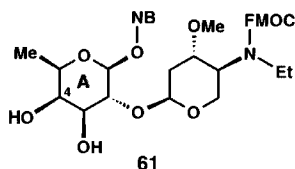
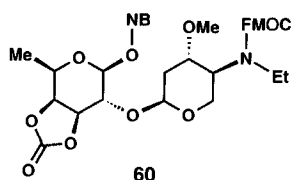
tative yield. Of the four acetate groups present in **58**, the anomeric acetate is particularly susceptible to cleavage. Indeed, treatment of **58** in a solution of $\text{CH}_2\text{Cl}_2/\text{acetic anhydride}$ with HBr in acetic acid furnishes a transient glycosyl bromide that is subsequently converted, in a completely stereoselective manner, into *ortho*-nitrobenzyl glycoside **59** under the conditions shown in Scheme 10. As expected, the C-2 acetate function guides the formation of the desired β -glycoside. In the triol revealed by solvolytic cleavage of the three acetate groups in **59**, two of the three contiguous hydroxyl groups reside on the same side of the pyran ring. On treatment with 1,1'-carbonyldiimidazole, these two hydroxyls can be simultaneously protected in the form of a five-membered cyclic carbonate, providing the targeted A-ring intermediate **19**. In this manner, the hydroxyl group at the 2-position can be made available for coupling with E-ring intermediate **20**.

Now with the two requisite coupling partners available, the next step is the elaboration of the AE ring system (see Scheme 11). Through the application of previously developed conditions for activation of glycosyl fluorides,²⁴ the convergent union of compounds **19** and **20** can be achieved, giving a 4.5:1 mixture of axial and equatorial isomers in favor of the desired axial glycoside **60** (ca. 70% yield).

To complete the synthesis of keto disaccharide **16**, the cyclic carbonate must be cleaved and the C-4 hydroxyl group must be oxidized selectively. With respect to the former objective, it is well known that a metal alkoxide (e.g. sodium methoxide) can easily



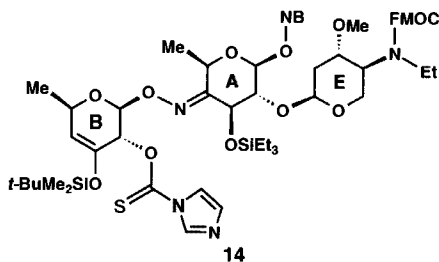
Scheme 11. Construction of oligosaccharide **8**: synthesis of intermediate **16**.

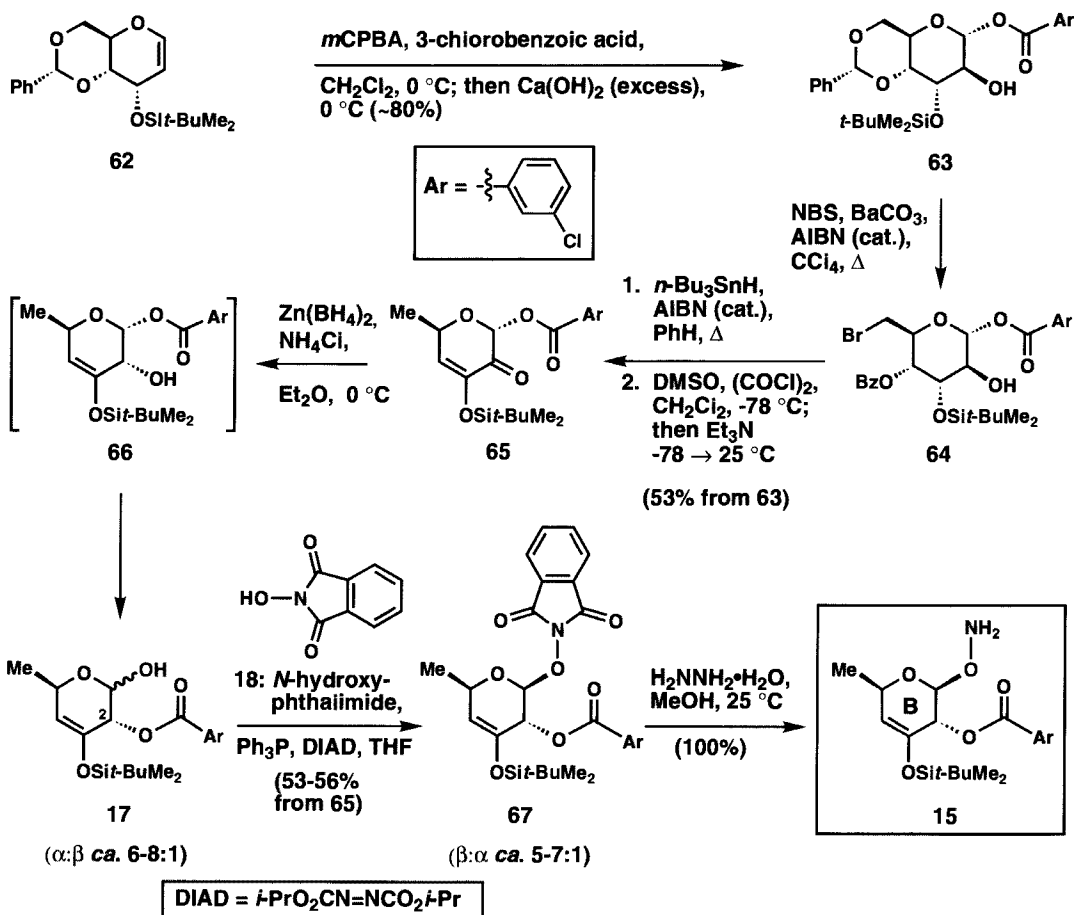


bring about the cleavage of a carbonate. In this context, however, the carbonate ring to be cleaved is contained within a molecule that also possesses the base-labile FMOC protecting group. Initial experiments with sodium methoxide in methanol demonstrated that the cyclic carbonate and FMOC protecting groups are removed with essentially equal facility. In contrast, treatment of a solution of **60** in THF-(CH₂OH)₂ (20:1) with a catalytic amount of sodium hydride at 0 °C results in the completely selective cleavage of the cyclic carbonate to give diol **61**; under these conditions, the potentially labile FMOC protecting group is not lost. It is presumed that the base-induced intermolecular attack of ethylene glycol upon the cyclic carbonate in **60** is followed by a facile intramolecular acyl migration reaction to give the diol product. Finally, regioselective oxidation of the C-4 hydroxyl group in ring A of **61** to the corresponding ketone (**16**) can be efficiently achieved using the David-Thieffry procedure.²⁵ This interesting regioselective transformation entails the formation of a stannylene ketal which is subsequently converted into the desired product by oxidation with bromine. Incidentally, tri-*n*-butyltin methoxide is added to quench the HBr liberated in the reaction.

The elaboration of B-ring intermediate **15** is presented in Scheme 12. Epoxidation of the known glycol **62**²⁶ with *meta*-chloroperoxybenzoic acid (*m*CPBA) with concomitant opening of the oxirane ring by 3-chlorobenzoic acid, generated *in situ*, provides intermediate **63** as a single stereoisomer. The yield for this transformation can be increased simply by adding small quantities of 3-chlorobenzoic acid to the reaction mixture. The benzylidene acetal moiety of **63** undergoes ready conversion to bromobenzoate **64** on treatment with *N*-bromosuccinimide (NBS), barium carbonate, and a catalytic amount of azobisisobutyronitrile (AIBN).²⁷ Reductive removal of the superfluous bromine atom in the conventional way with tri-*n*-butyltin hydride and a catalytic amount of AIBN, followed by a Swern oxidation²⁹ furnishes enone **65**. In the latter reaction, the oxidation of the C-2 alcohol to the corresponding ketone is attended by β -elimination of the C-4 benzoate ester function. Multigram quantities of enone **65** can be prepared by this four-step sequence.

A key feature of the oligosaccharide synthesis strategy outlined in Scheme 4 is the projected [3,3] sigmatropic rearrangement of O-bound imidazolethiocarboxylate **14**; if successful, this transformation would accomplish the stereospecific introduction of sulfur at position 4 in ring B and the necessary deoxygenation at C-2. *A priori*, the critical oxygen-bearing stereocenter at the 2-position of ring B in **14** could be created by reduction of the keto group in enone **65** (Scheme 12). Actually, it would be imperative to achieve a diastereoselective ketone reduction because asymmetry is transferred from the 2-position of ring B to the 4-position during the course of the suprafacial sigmatropic process discussed previously. To accomplish the task of reducing enone **65** stereoselectively, a number of reagents were surveyed. For example, Luche reduction (NaBH₄, CeCl₃•7H₂O, MeOH) of enone **65** furnishes lactol **17** as a



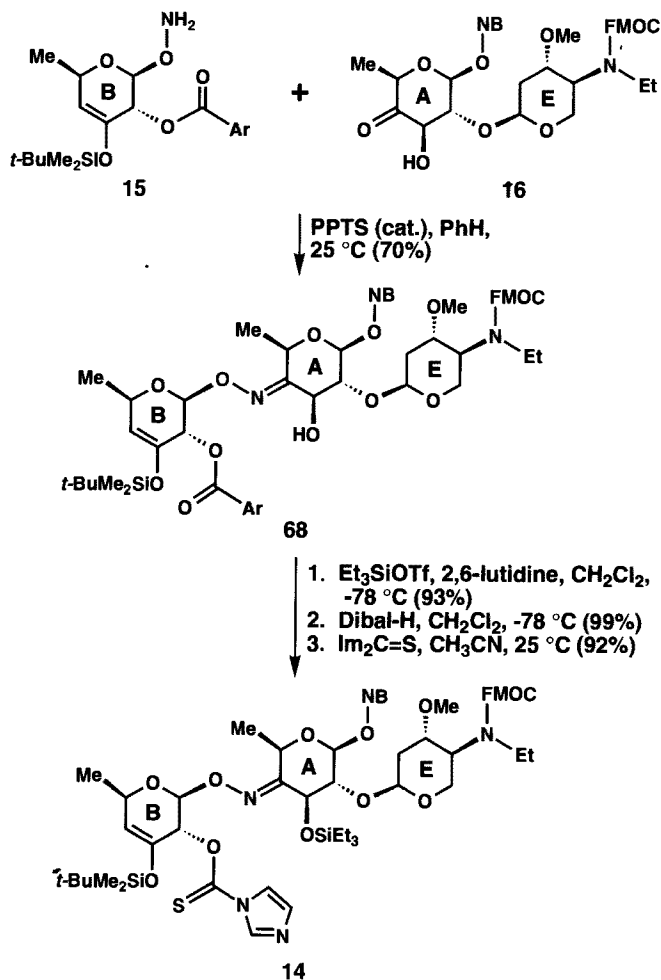


Scheme 12. Construction of oligosaccharide **8**: synthesis of intermediate **15**.

1:1 stereoisomeric mixture of α - and β -anomers (69% yield). Although intermediate **66** can be detected by TLC analysis, it is not isolable; once formed, **66** participates in an acyl migration reaction to give, after epimerization of the anomeric center, compound **17**. Since it has a C-2 benzoate ester arranged properly in space, **17** would appear to be an ideal candidate for a β -selective glycosidation reaction, provided of course that the anomeric position can be activated. Surprisingly, subjection of the equimolar mixture of lactol isomers to a Mitsunobu glycosidation with *N*-hydroxyphthalimide (**18**) as the glycosyl acceptor provides a 1:1 mixture of α - and β -glycosides **67** in 92% yield. If a 3:1 mixture of α - and β -lactols **17** is employed in the same reaction, a ratio of products corresponding to inversion of the anomeric center is obtained. This result suggests that the intermediate oxyphosphonium ion does not dissociate to form an oxonium ion prior to attack by the nucleophile. Under these circumstances, the adjacent ester

function would not have the opportunity to control the stereochemical course of the glycosidation reaction through anchimeric assistance.

If it is assumed that the Mitsunobu glycosidation reaction described above proceeds through an S_N2 -type process with inversion of configuration at the anomeric position, then it follows that the desired β -glycoside can be formed selectively if pure α -lactol **17** is used in the reaction. Unfortunately, the β -lactol isomer of **17** is thermodynamically more stable than the α -diastereoisomer and is formed almost exclusively if the system is allowed to fully equilibrate. In the protic medium used for the Luche reduction, a signifi-

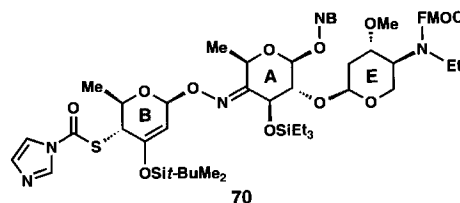
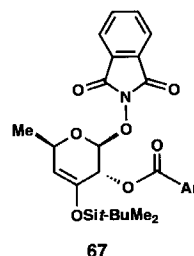
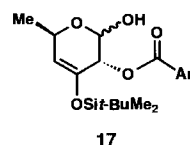
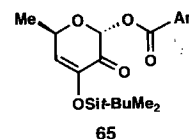


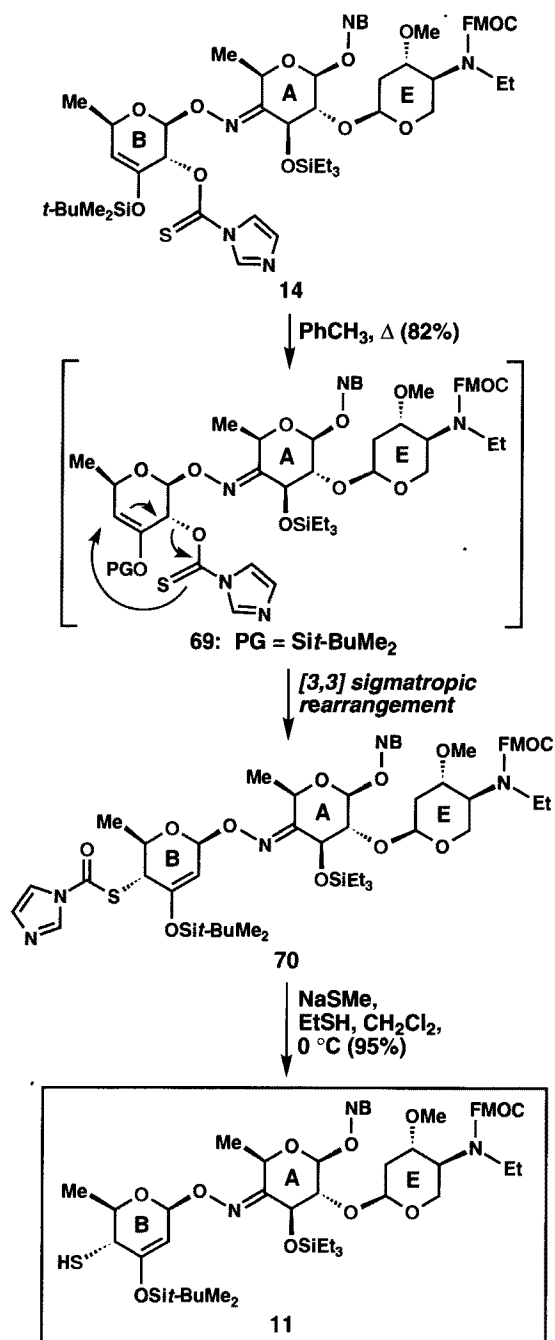
Scheme 13. Construction of oligosaccharide **8**: synthesis of intermediate **14**.

cant proportion of the α -lactol isomer, which forms initially from the acyl migration reaction (see **66** \rightarrow **17a**, Scheme 12), undergoes conversion to the unwanted β -lactol isomer. On the other hand, treatment of enone **65** with zinc borohydride in diethyl ether at 0°C furnishes **17** as a 6:1 to 8:1 mixture of α - and β -lactols in favor of the desired α -isomer (see Scheme 12). Apparently, when ether is used as the solvent for the reduction, the configuration of the anomeric position can be more easily preserved. Incidentally, ammonium chloride is added to the reaction mixture to inhibit silyl group migration. With the stereochemistry of lactol **17** well preserved (α : β ca. 6:1 to 8:1), the ratio of the β -glycoside **67** formed in the Mitsunobu glycosidation can be increased to between 5:1 and 7:1, with an overall yield of 53–56% from enone **65** (see Scheme 12). The completion of the synthesis of B-ring intermediate **15** only requires cleavage of the phthalimide function, a task easily achieved by treatment of **67** with hydrazine (100% yield).

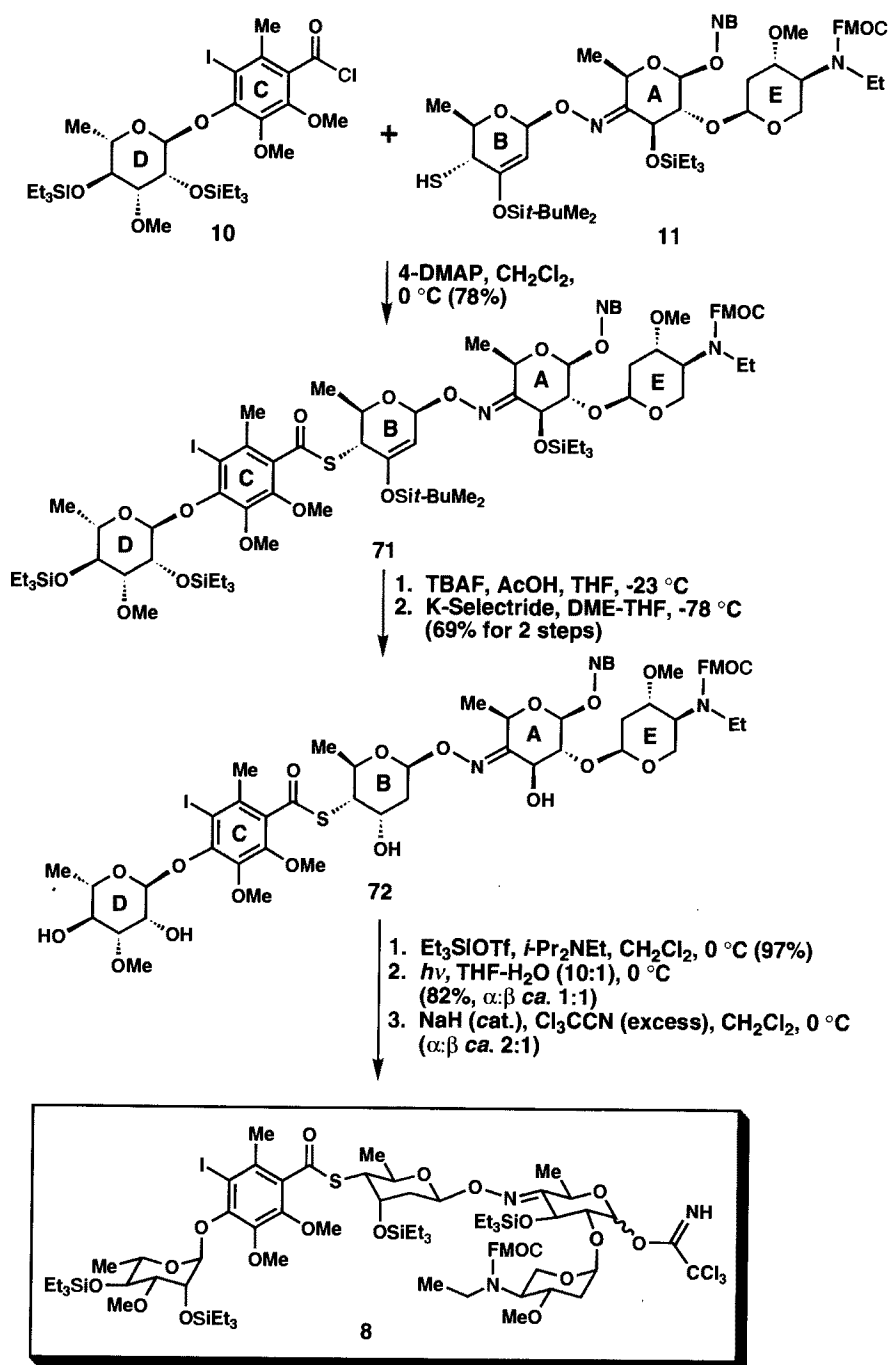
With key intermediates **15** and **16** in hand, we are now in a position to address their union and the elaboration of imidazolethiocarboxylate **14** (see Scheme 13). You will note that compounds **15** and **16** possess complementary sites of reactivity. It was anticipated that the free amino function in **15** could be induced to converge upon the electrophilic ketone carbonyl in **16** under sufficiently mild conditions to give, after loss of a water molecule, a functionalized tricyclic oxime ether. Indeed, exposure of a mixture of compounds **15** and **16** in benzene at 25°C to a catalytic amount of pyridinium *para*-toluenesulfonate (PPTS) results in the formation of oxime ether **68**. This convergent coupling reaction furnishes a single oxime stereoisomer; although a particular geometrical isomer is illustrated in Scheme 13, this assignment was not confirmed. Quantitative triethylsilylation of the free hydroxyl group in **68** with triethylsilyl triflate, followed sequentially by reductive cleavage of the B-ring benzoate with Dibal-H and acylation of the liberated hydroxyl group with 1,1'-thiocarbonyldiimidazole, completes the synthesis of key intermediate **14**. It is noteworthy that the Fmoc protecting group is not cleaved at any point along the path from **68** to **14**.

A critical stage in the synthesis of the oligosaccharide domain of calicheamicin γ_1^I (**1**) has been reached. Having retraced the sequences of reactions that have culminated in the synthesis of key intermediate **14**, we are in a position to address the crucial [3,3] sigmatropic rearrangement (see Scheme 14). Although Ferrier's demonstration that allylic xanthates can be induced to undergo [3,3] sigmatropic rearrangements provides important precedent for this type of transformation,²⁸ the [3,3] sigmatropic rearrangement of an allylic imidazolethiocarboxylate system containing a silyl enol ether had, to the best of our knowledge, not been previously demonstrated. Nevertheless, on the basis of some successful model studies,^{7d} a good deal of confidence was invested in the proposition that allylic O-bound imidazolethiocarboxylate **14** could be converted into the S-bound isomer **70** via a [3,3] sigmatropic rearrangement. Indeed, when a solution of **14** in toluene is heated to reflux

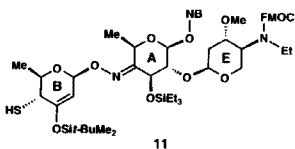




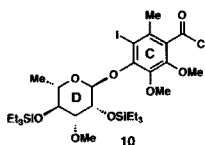
Scheme 14. Construction of oligosaccharide **8**: synthesis of intermediate **11**.



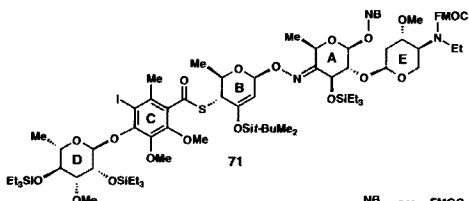
Scheme 15. Synthesis of oligosaccharide 8.



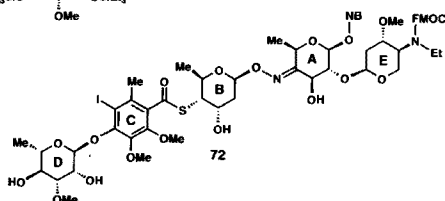
11



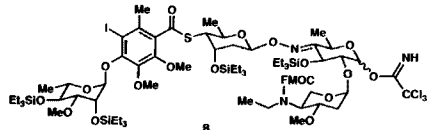
10



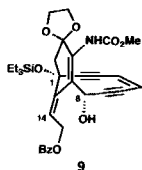
71



72



8



9

for about 45 minutes, the desired rearrangement takes place smoothly, giving **70** in 82% yield. In one productive step, the sulfur atom at position 4 of ring B is introduced stereospecifically and the necessary deoxygenation at position 2 is achieved. Cleavage of the imidazolethiocarboxylate with sodium methanethiolate in the presence of ethanethiol provides thiol **11** in nearly quantitative yield. Multigram quantities of trisaccharide **11** can be prepared by the reaction sequences described.

Although it is likely that the electron-rich aromatic ring in compound **10** reduces the electrophilic character of the carbonyl carbon, acid chloride **10** and thiol **11** combine smoothly and in the expected way to give intermediate **71** in 78% yield (see Scheme 15). This convergent acylation reaction accomplishes the formation of a molecule that possesses all five rings of the targeted oligosaccharide. The potentially difficult task of achieving the stereoselective formation of the oxygen-bearing stereocenter at the 3-position of ring B must be mastered before the synthesis of key intermediate **8** can be accomplished. To this end, cleavage of the *tert*-butyldimethylsilyl enol ether in **71** with tetra-*n*-butylammonium fluoride (TBAF) and acetic acid furnishes an unstable ketone that can be reduced in a stereoselective fashion with potassium tri-*sec*-butylborohydride (K-Selectride) to give the desired alcohol **72** (69% overall yield). Triethylsilylation of the hydroxyl groups in **72** with triethylsilyl triflate, followed by photolytic cleavage of the *ortho*-nitrobenzyl protecting group, furnishes a 1:1 mixture of A-ring lactols. Finally, treatment of the equimolar mixture of lactols with excess trichloroacetonitrile in the presence of a catalytic amount of sodium hydride according to Schmidt's procedure^{8d,10} furnishes key intermediate **8** as a 2:1 mixture of α - and β -anomers in high yield.

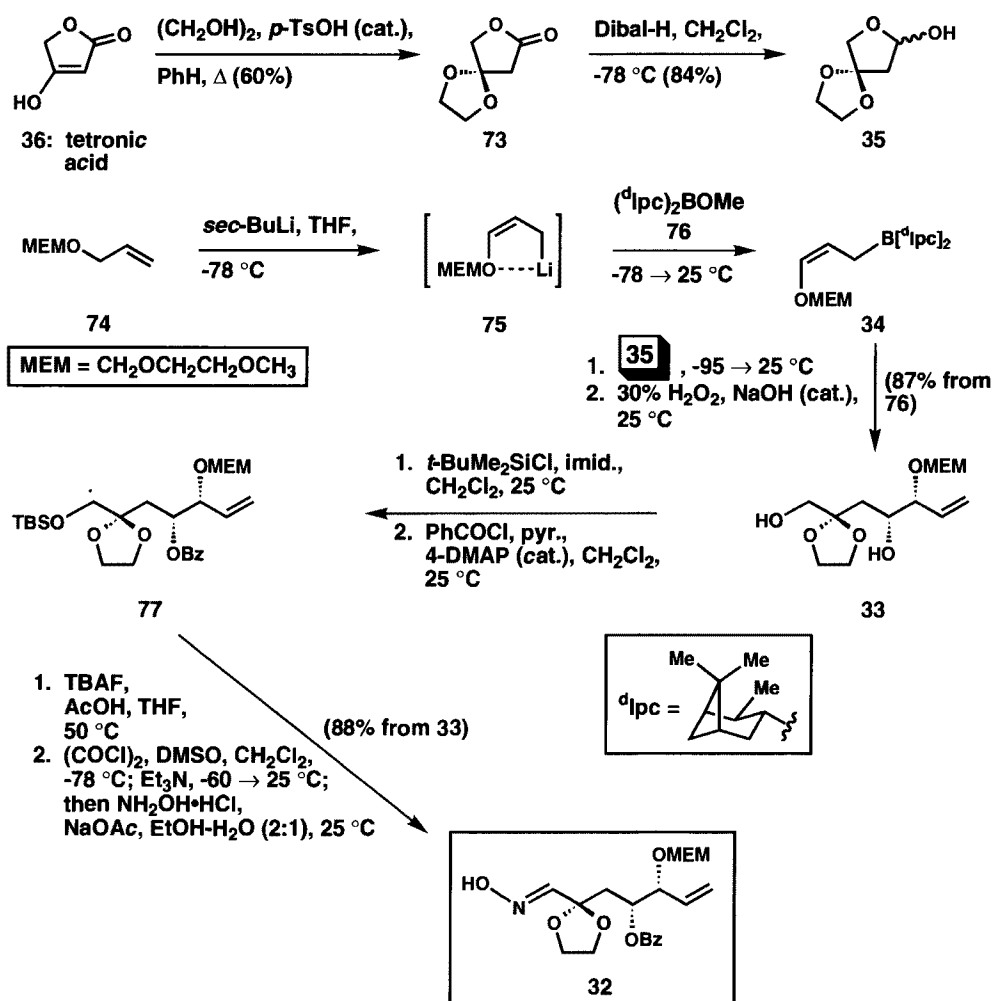
30.3.2 Synthesis of Aglycon **9**

Schemes 16–19 present the details of the enantioselective synthesis of key intermediate **9**. The retrosynthetic analysis outlined in Scheme 5 identified aldoxime **32** as a potential synthetic intermediate; the construction of this compound would mark the achievement of the first synthetic objective, for it would permit an evaluation of the crucial 1,3-dipolar cycloaddition reaction. As it turns out, an enantioselective synthesis of aldoxime **32** can be achieved in a straightforward manner by a route employing commercially available tetronic acid (**36**) and the MEM ether of allyl alcohol (**74**) as starting materials (see Scheme 16).

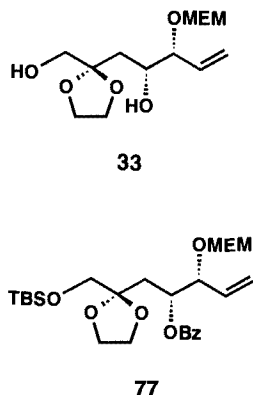
Ketal **73** can be formed in a yield of about 60% by refluxing a solution of tetronic acid (**36**), ethylene glycol, and a catalytic amount of *para*-toluenesulfonic acid in benzene for approximately 12 hours. With only one electrophilic site, **73** reacts smoothly with Dibal-H to give lactol **35** in 84% yield. Compound **35**, a participant in a ring-chain tautomeric equilibrium process,¹⁸ should be regarded as a latent aldehyde. This substance can, in fact, serve as

an electrophile in an intermolecular coupling reaction with enantiomerically pure (*Z*) γ -alkoxyallylborane **34**. The latter intermediate can be fashioned in only two steps from the MEM ether of allyl alcohol (see Scheme 16) by means of Brown's procedure,¹⁷ and it combines smoothly and stereoselectively with the open-chain aldehyde form of **35** to give intermediate **33** in 87% yield after oxidative workup. This coupling reaction exhibits exceptional *syn* diastereoselectivity (>98% as determined by ¹H NMR analysis) and can be conducted on a large scale.

It will be noted that intermediate **33** contains all of the carbon atoms and the two stereocenters of the targeted aldoxime **32**. At the outset, it was anticipated that the terminal oxime function in **32** could be formed by the condensation of hydroxylamine with the

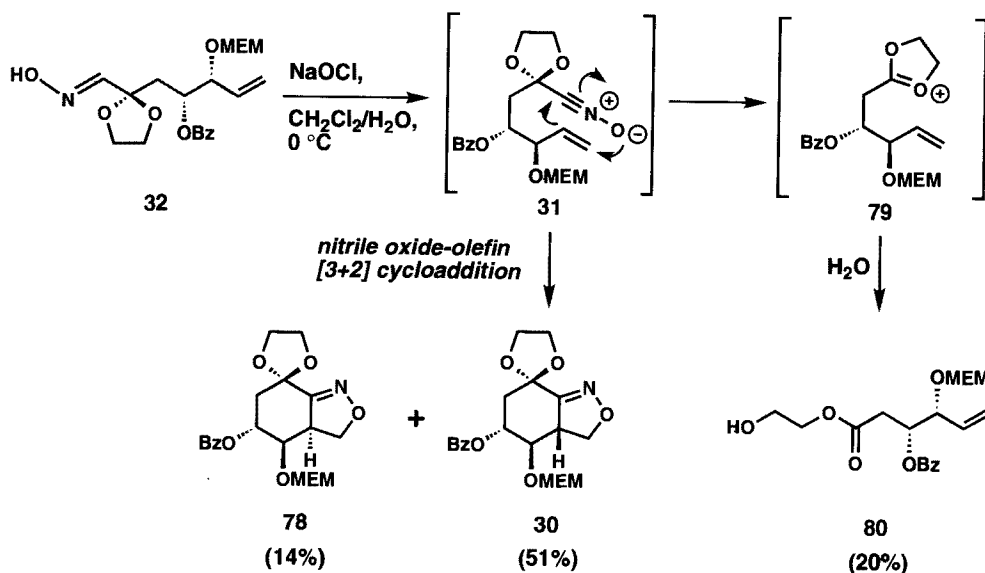


Scheme 16. Construction of aglycon **9**: synthesis of intermediate **32**.



aldehyde derived through oxidation of the primary alcohol in **33**. Although a selective oxidation of the primary alcohol in **33** can be performed, the production of a five-membered lactol and/or lactone cannot be avoided. It is, therefore, necessary to protect the secondary hydroxyl group so that the desired oxidation can be achieved. Selective silylation of the primary hydroxyl group in **33** with *tert*-butyldimethylsilyl chloride, followed by benzylation of the secondary hydroxyl, furnishes intermediate **77**. The desired primary alcohol can then be produced by cleavage of the *tert*-butyldimethylsilyl ether with TBAF buffered with acetic acid. Although this three-step diprotection-deprotection sequence may seem circuitous, the yield for each step is essentially 100%, and there is no need for chromatographic purification of intermediates. With the secondary hydroxyl group suitably protected in the form of a benzoate ester, the desired oxidation can be effected by the Swern procedure.²⁹ For convenience, addition of hydroxylamine hydrochloride to the Swern mixture during workup results in the formation of aldoxime **32** as a single geometrical isomer (geometry not determined) in an overall yield of 88% from diol **33**.

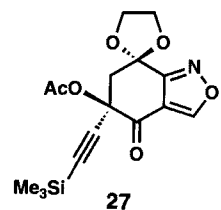
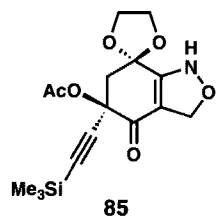
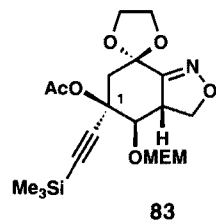
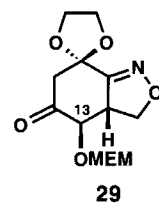
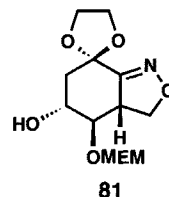
The intramolecular cycloaddition of a nitrile oxide (a 1,3-dipole) to an alkene is ideally suited for the regio- and stereocontrolled synthesis of fused polycyclic isoxazolines.¹⁶ The simultaneous creation of two new rings and the synthetic versatility of the isoxazoline substructure contribute significantly to the popularity of this cycloaddition process in organic synthesis. In spite of its high degree of functionalization, aldoxime **32** was regarded as a viable substrate for an intramolecular 1,3-dipolar cycloaddition reaction. Indeed, treatment of **32** (see Scheme 17) with sodium hypochlorite

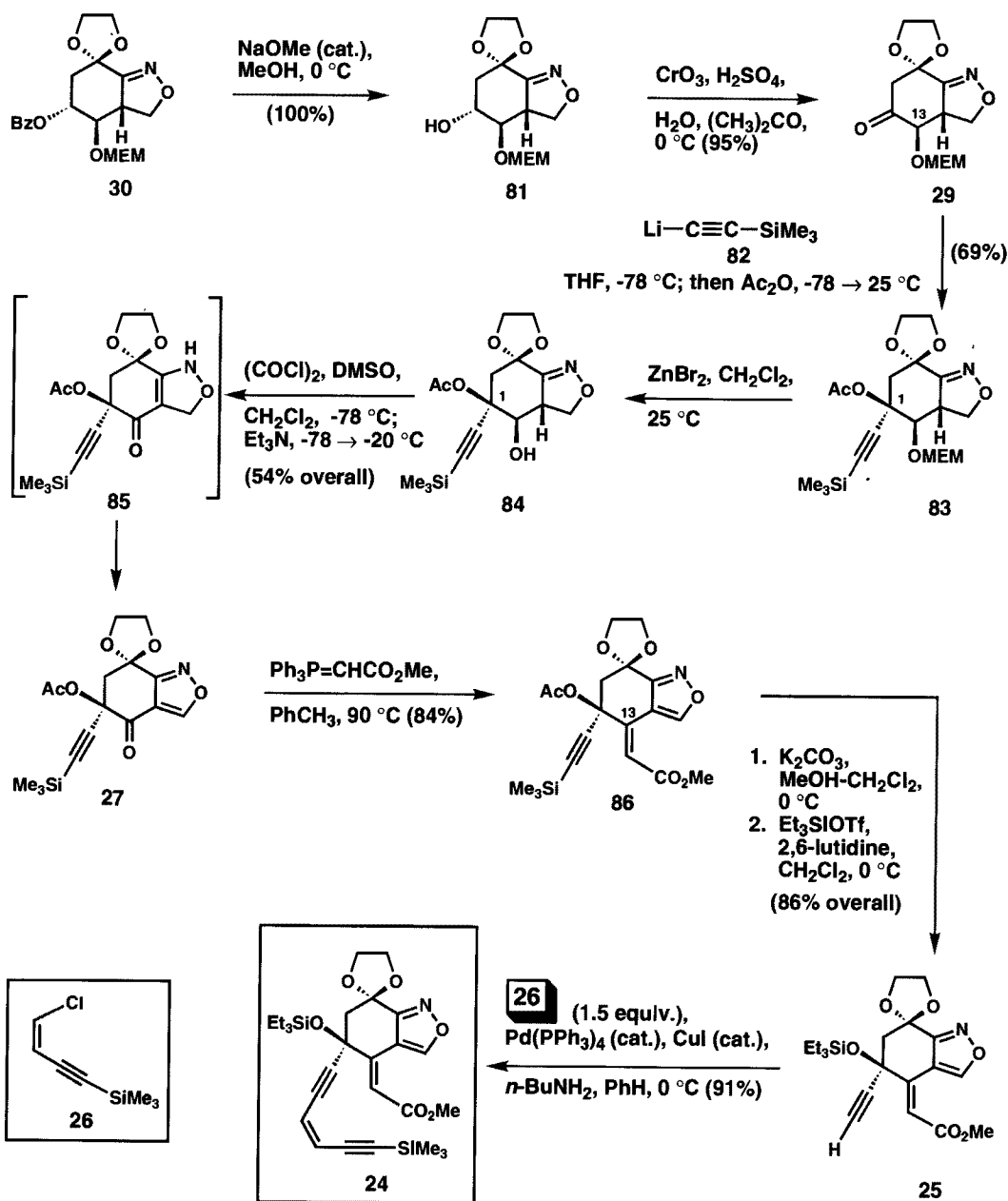


Scheme 17. Construction of aglycon **9**: intramolecular nitrile oxide–olefin cycloaddition of intermediate **31**.

at 0 °C results in the formation of two fused bicyclic isoxazolines, **30** and **78**, in 65 % overall yield (**30:78** ca. 3.5:1) together with 20 % of acyclic unsaturated ester **80**. It is presumed that the action of sodium hypochlorite on **32** generates, through the intermediacy of an α -chloroaldehyde, unsaturated nitrile oxide **31**. This substance is not isolated; once formed, it readily participates in the desired 1,3-dipolar cycloaddition reaction to give a ca. 3.5:1 diastereomeric mixture of isoxazolines **30** and **78**. Unsaturated ester **80** presumably arises from the decomposition of nitrile oxide **31**, a process that is likely induced by one of the adjacent ketal oxygen atoms (see **31** \rightarrow **79** \rightarrow **80**, Scheme 17). *A priori*, both bicyclic isoxazoline epimers could be utilized in this synthesis because the newly formed stereocenter is eventually destroyed. Nevertheless, the two isoxazoline diastereomers were separated, and the subsequent stages of the synthesis were defined using the major isomer **30**.

Solvolytic cleavage of the benzoate ester in **30** with sodium methoxide in methanol, followed by Jones oxidation of the resulting secondary alcohol **81**, provides ketone **29** in 95 % overall yield (see Scheme 18). Ketone **29** is a rather fragile substance that undergoes facile β -elimination in the presence of basic reagents and even silica gel. The β -disposed MEM ether at C-13 in **29** is a valuable structural feature; it was hoped that the steric bulk of this substituent would direct the addition of an acetylide anion to the less congested diastereoface of the ketone. In the event, addition of lithium (trimethylsilyl)acetylide (**82**) to a cold (–78 °C) solution of ketone **29** in THF, followed by treatment of the carbonyl addition product with acetic anhydride, provides tertiary acetate **83**. The β -disposed MEM ether evidently creates a strong diastereofacial bias because **83** is the only stereoisomer formed. Having served its dual purpose as a protecting group and as a stereocontrolling device, the MEM ether at C-13 must now be cleaved. Although compound **83** contains functionality that could be compromised in the presence of strong Lewis acids, the desired cleavage can be brought about with zinc bromide³⁰ at 25 °C (see **83** \rightarrow **84**, Scheme 18). Not surprisingly, alcohol **84** must be handled carefully in order to prevent migration of the tertiary acetyl group onto the adjacent secondary hydroxyl. With the fully substituted stereocenter at C-1 correctly in place, the next major task to be addressed is the construction of the exocyclic α,β -unsaturated ester at C-13. It was envisioned that this objective might be achieved via an intermolecular Wittig reaction between a stabilized phosphorus ylide and the ketone derived through oxidation of secondary alcohol **84**. Reduction of this general plan to practice was not without incident, however. For example, under the conditions of a Swern oxidation, the secondary alcohol in **84** undergoes ready conversion to the corresponding ketone. But in addition to this desired and expected change, the isoxazoline ring undergoes isomerization to a putative vinylogous amide (see **85**), which could conceivably be converted to isoxazole **27** through aerial oxidation. Although this productive transformation was not predicted entirely, it is nonetheless very useful. You will note that





Scheme 18. Construction of aglycon **9**: synthesis of intermediate **24**.

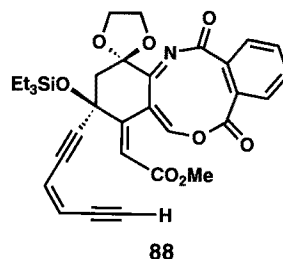
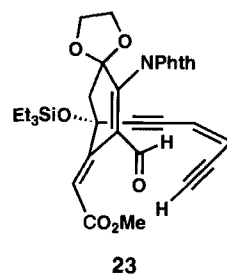
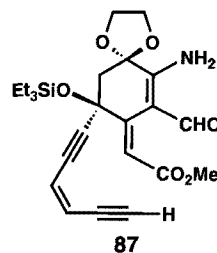
the isoxazole ring in **27** harbors, in latent form, the amine, aldehyde, and double bond functions that are required for the projected cyclization substrate **23** (see Scheme 5).

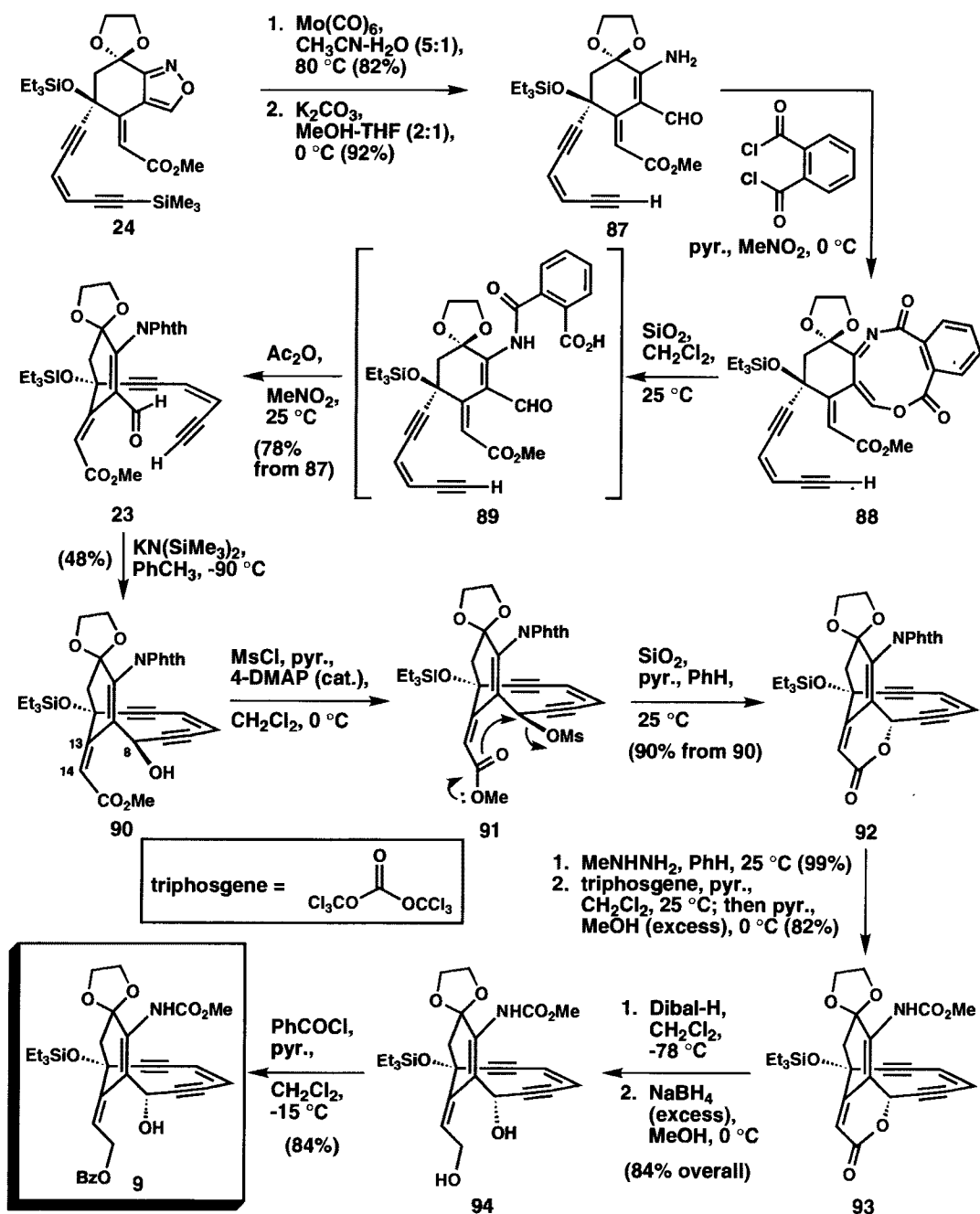
Despite its hindered nature, keto isoxazole **27** (Scheme 18) reacts smoothly with methyl (triphenylphosphoranylidene)acetate at 90 °C in toluene solution to give the desired α,β -unsaturated ester **86** in 84 % yield. Gratifyingly, **86** is formed as a single geometrical isomer. It was anticipated that the newly introduced methoxycarbonyl function would serve as a convenient handle for the later introduction of the trisulfide moiety.

With the exocyclic alkylidene at C-13 properly in place, the elaboration of the 1,5-diyne-3-ene moiety can now be addressed. Cleavage of both acetate and trimethylsilyl functions in **86** with basic methanol, followed by triethylsilylation of the newly formed tertiary hydroxyl group, efficiently affords alkyne **25** (86 % overall yield). This substance was regarded as a viable candidate for a Pd-catalyzed coupling reaction.¹² Indeed, treatment of **25** with (*Z*)-chloroenyne **26** in the presence of a catalytic amount of Pd(PPh₃)₄ and Cu^I results in the formation of enediyne **24** in 91 % yield.

Although a number of reagents can be used to reduce an isoxazole ring, molybdenum hexacarbonyl³¹ was selected for use in this synthesis. The action of this reagent on **24** reduces the weak N–O bond of the isoxazole ring and produces a β -amino- α,β -unsaturated aldehyde (i.e. a vinylogous formamide) (see Scheme 19). Intermediate **87** forms smoothly upon deprotection of the terminal acetylene carbon with basic methanol–THF.

At first glance, compound **87** might appear to be well suited for the crucial intramolecular carbonyl addition reaction; after all, it possesses an electrophilic aldehyde carbonyl and a potentially nucleophilic alkyne moiety. However, the primary amino group in **87**, itself a strong electron-releasing substituent, is conjugated with the aldehyde carbonyl. Delocalization of the lone pair on the nitrogen atom would be expected to attenuate the electrophilicity of the aldehyde carbonyl, thereby reducing its susceptibility to an attack by a nucleophile. The action of a basic reagent on **87** would most likely result in rapid deprotonation of the enamino function, and delocalization of the resulting anion would reduce, even further, the electrophilic character of the aldehyde carbonyl. Thus, before the crucial cyclization reaction can be performed, the free amino function in **87** must be masked. Protection of this group in the form of a phthalimide appeared particularly attractive because it would allow both of the acidic amino hydrogens to be replaced. Moreover, as a phthalimide, the enamino nitrogen atom would be expected to be a much weaker electron donor. This task could, in principle, be achieved by treatment of **87** with phthaloyl chloride. Although small quantities of the desired *N*-protected compound (see **23**) can be obtained in this manner, by far the major product formed is the novel nine-membered heterocycle **88**. Fortunately, this compound is labile and undergoes ready hydrolysis on silica gel to give a phthalic acid derivative **89**. Activation of the free carboxyl function

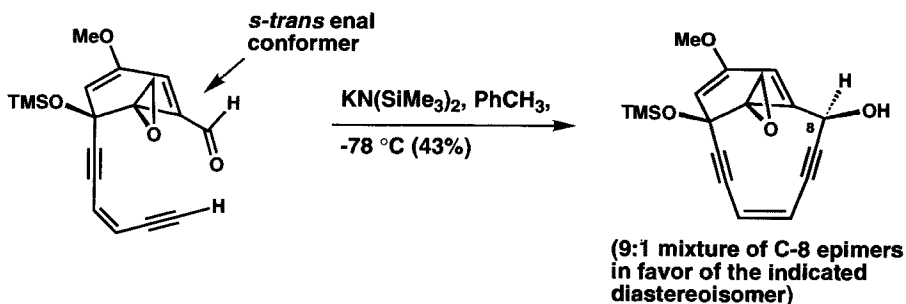




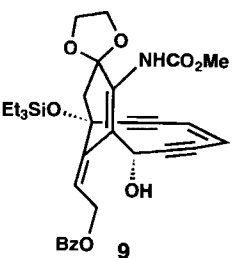
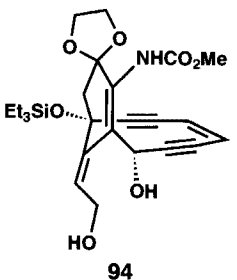
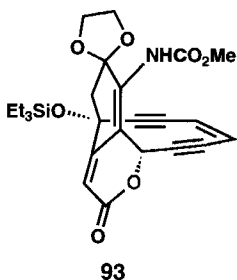
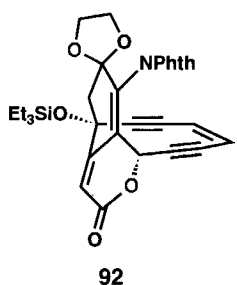
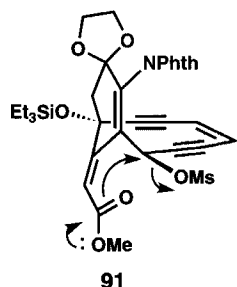
Scheme 19. Synthesis of aglycon 9.

in **89** in the form of a mixed anhydride is attended by cyclization to give the desired phthalimide protected compound **23** (78 % yield from **87**).

With the β -amino function in a suitably protected form, the construction of calicheamicin's strained, polyunsaturated ten-membered ring can be addressed. On the basis of previous results^{32,33} (see Scheme 20), it was projected that ring closure could be induced by treatment of **23** with a strong nonnucleophilic base, and that a 1,2-addition of the acetylide to an *s-trans* enal would result in the formation of the desired C-8 epimer. In the event, exposure of **23** to freshly prepared potassium bis(trimethylsilyl)amide (from KH and $\text{HN}(\text{SiMe}_3)_2$) results in the formation of compounds **90** and **92** in a ratio of approximately 3.8:1 (48 % total yield). This unexpected result is consistent with a preferred intramolecular attack of the acetylide upon an *s-cis*, rather than an *s-trans*, enal. The production of **90** as the major product was, at first, regarded as disastrous because all attempts to invert the errant stereocenter at C-8 through the use of traditional intermolecular inversion techniques such as the Mitsunobu reaction were wholly unsuccessful. When faced with a problem of this type, one should be mindful of an important principle in organic synthesis enunciated in the following quotation by Albert Eschenmoser: "Whenever in the synthesis of complex organic molecules one is confronted with a situation where the success of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look out for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly."³⁴ Analysis of the structure of **90** reveals that the methoxycarbonyl group and the hydroxyl-bearing carbon (C-8) reside in neighboring regions of space by virtue of the *trans* $\Delta^{13,14}$ double bond geometry. In the event that the C-8 secondary hydroxyl group in **90** can be converted into a more suitable leaving group, it may be possible to coax the Lewis-basic methoxycarbonyl group to initiate an intramolecular $\text{S}_{\text{N}}2$ -type



Scheme 20. The intramolecular carbonyl addition reaction used by Danishefsky and coworkers to construct a 10-membered ring enediyne system.



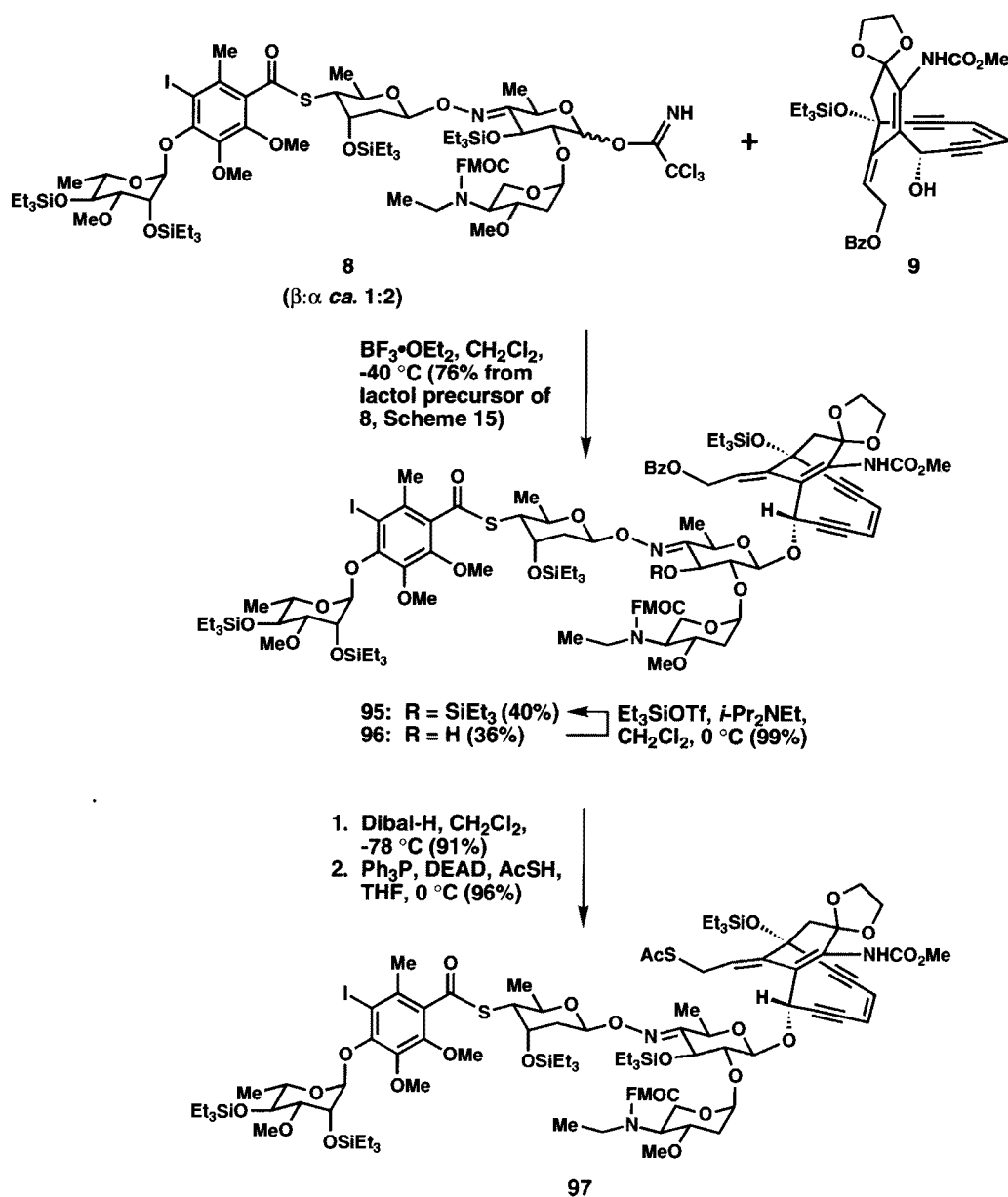
displacement with inversion of configuration at C-8. Despite its hindered nature, the C-8 hydroxyl group in **90** can be converted into mesylate **91** on treatment with methanesulfonyl chloride and pyridine; it was hoped that the propargylic mesylate in **91** could be induced to depart with assistance by the proximal methoxycarbonyl group. As it turns out, if a solution of **91** in benzene is simply treated with silica gel and pyridine at 25°C, the desired lactonization takes place with exceptional facility to give lactone **92**, the same substance produced as the minor product in the intramolecular carbonyl addition reaction (see **23** → **90**+**92**, Scheme 19). It is noteworthy that the crucial intramolecular displacement reaction proceeds with complete inversion of configuration at C-8. It should also be noted that pyridine is an essential additive in this reaction; pyridine functions as a base to scavenge the methanesulfonic acid that is produced as a by-product. Partial hydrolysis of the silyl ether and the ethylene ketal takes place if pyridine is not added to the reaction mixture.

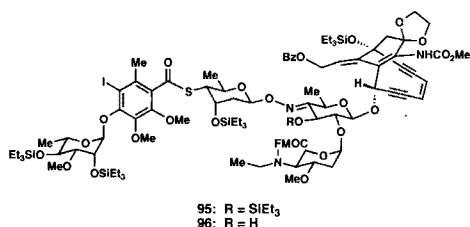
The completion of the synthesis of key intermediate **9** only requires a few straightforward functional group manipulations. Thus, cleavage of the phthalimide protecting group in **92** with methyl hydrazine provides, in nearly quantitative yield, a primary enamine that can be converted to methyl carbamate **93** by the sequential action of triphosgene and methanol. Reduction of the δ -lactone carbonyl with Dibal-H furnishes a mixture of lactol diastereomers, both of which undergo conversion to diol **94** on treatment with NaBH₄. Finally, selective benzylation of the less hindered primary hydroxyl group in **94** with benzoyl chloride proceeds smoothly and gives key intermediate **9** in 71% overall yield from **93**. Although small amounts of a dibenzoate are formed in the latter reaction, this compound can be converted back to diol **94** for recycling, by reduction with excess Dibal-H.

30.3.3 Coupling of Intermediates **8** and **9** and Completion of the Total Synthesis of Calicheamicin γ_1^I

Another critical stage in the synthesis has been reached. The previous sections have summarized the reactions leading to the synthesis of both domains of calicheamicin γ_1^I , each with the correct absolute stereochemistry and in a form suitable for further advance. We are now in a position to describe the union of key intermediates **8** and **9** (see Scheme 21).

It will be recalled that the retrosynthetic analysis outlined in Scheme 3 identified the Schmidt glycosidation reaction as a potential process for joining fragments **8** and **9**. Schmidt's protocol is ideally suited for the construction of glycosidic bonds, and its utility has been amply demonstrated in a variety of contexts.^{8d-e,35,36} Gratifyingly, treatment of a cooled (−40°C) solution of **8** (1 equivalent) and **9** (1.4 equivalents) in dry CH₂Cl₂ with BF₃•OEt₂ (3 equivalents) affords the desired β -glycoside **95** in 40% yield

Scheme 21. Synthesis of intermediate **97**.

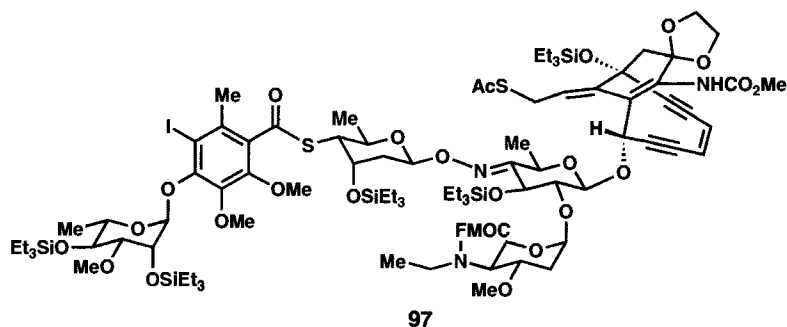


together with the monodesilylated β -glycoside **96** (36 % yield). It is significant that none of the undesired α -glycoside could be detected in this crucial coupling step. Fortunately, compound **96** can be converted quantitatively to **95** through silylation under standard conditions raising the total yield of **95** to 76 %.

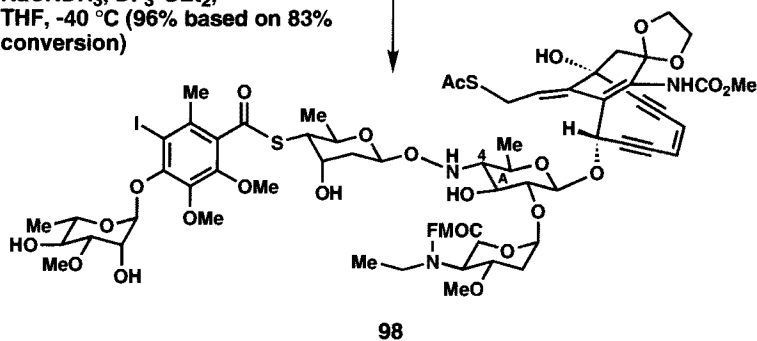
With the two domains of the natural product joined through a β -glycosidic bond, attention can now be turned to the nontrivial tasks of reducing the oxime ether function stereoselectively and installing the sensitive trisulfide moiety. Careful treatment of **95** with Dibal-H accomplishes the reductive cleavage of the benzoate ester, furnishing a free allylic alcohol (91 % yield). The stability of the thiobenzoate function in the presence of Dibal-H is noteworthy and is attributed to its highly hindered nature. Now, when this newly formed allylic alcohol is subjected to a Mitsunobu reaction with thioacetic acid, the allylic hydroxyl group is smoothly replaced by a thioacetate group to give intermediate **97**. This efficient transformation was known from the work of Danishefsky and his group at Yale,³² and it performed admirably in this synthesis. The introduction of the first of the three sulfur atoms of the trisulfide moiety has been accomplished.

At this stage of the synthesis, it was decided to contend with the oxime ether reduction problem (see Scheme 22). After cleavage of all five triethylsilyl ethers in **97** with excess HF•pyridine, exposure to sodium cyanoborohydride and BF₃•OEt₂ results in a completely chemo- and modestly stereoselective reduction of the A-ring carbon–nitrogen double bond, providing a 2:1 mixture of stereoisomers in favor of the desired C-4 α -epimer **98**. Chromatography of the crude reaction mixture on silica gel allows the separation of **98** from the stereoisomeric β -epimer, but not from unreduced oxime pentol starting material. This unfortunate circumstance necessitated a careful purification step at a later stage in the synthesis. To minimize the occurrence of undesired side reactions during subsequent transformations, it was deemed necessary to protect the free hydroxyl groups in intermediate **98**. To this end, treatment of **98** with excess quantities of triethylsilyl triflate and Hünig's base accomplishes the silylation of the five free hydroxyl groups. This seemingly straightforward modification is, however, not without intrinsic interest. When the reaction mixture was examined by thin layer chromatography, a long streak was observed. It was surmised that during the course of the persilylation reaction, the A-ring N atom attached to C-4 in **98** undergoes silylation as well, and that the resulting *N*-silyl compound decomposes slowly on silica gel. Fortunately, the N–Si bond is labile and can be easily cleaved upon treatment of the crude product with aqueous acetic acid in ethyl acetate.

With the free hydroxyl groups in a suitably protected form, the introduction of the reactive allylic trisulfide triggering device can be addressed. When this advanced stage of the synthesis was reached, it was already known from the work of Magnus³⁷ that the calicheamicin-type allylic methyl trisulfide can be formed upon

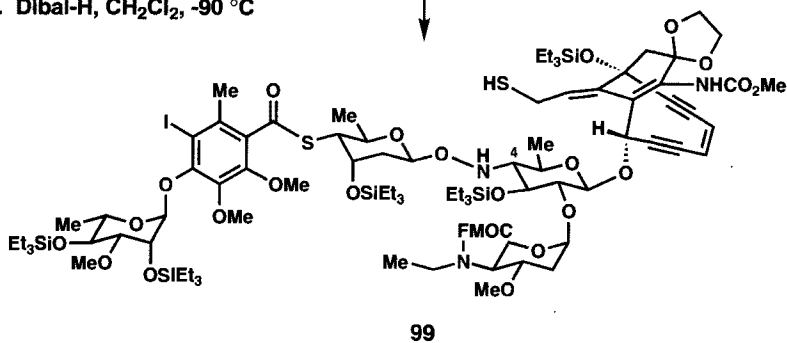


1. HF·pyr. (excess), THF-CH₂Cl₂ (6:1), 0 → 25 °C (94%)
2. NaCNBH₃, BF₃·OEt₂, THF, -40 °C (96% based on 83% conversion)



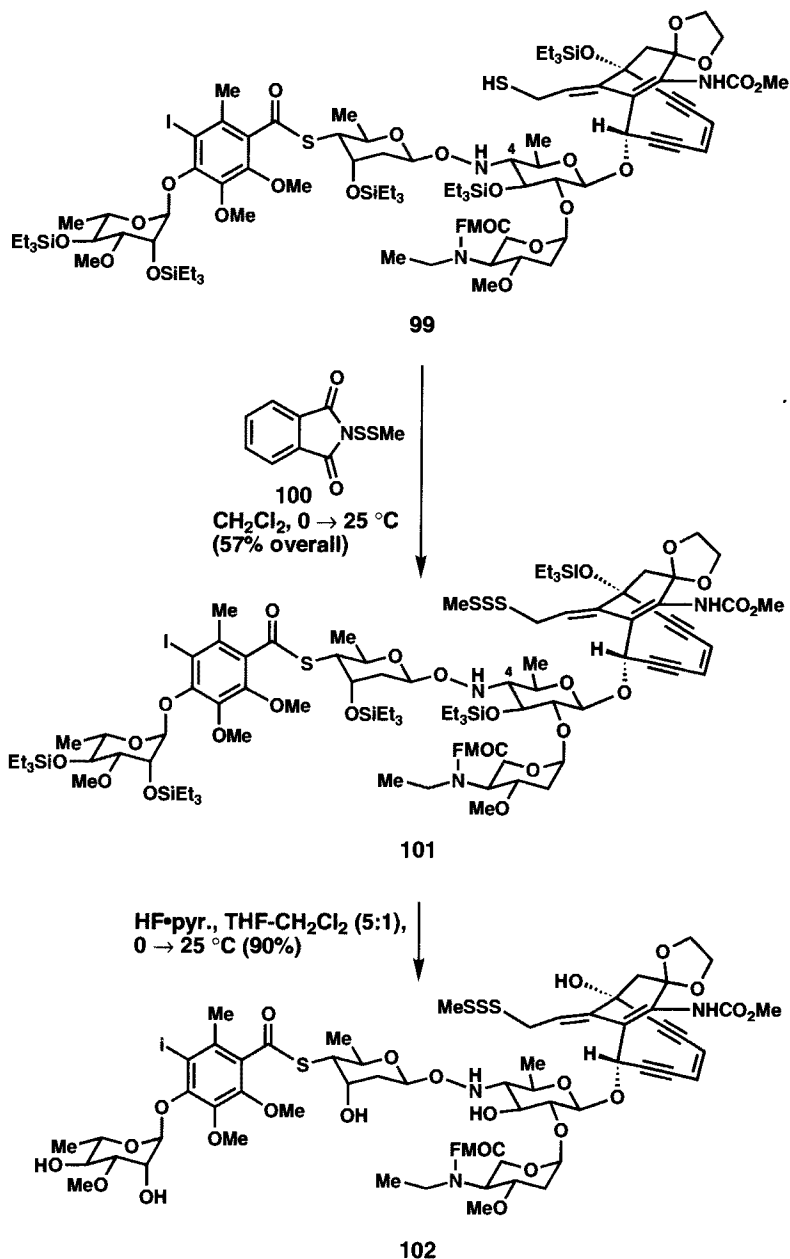
(2:1 mixture of C-4 epimers in favor of 98)

1. Et₃SiOTf, *i*-Pr₂NEt, CH₂Cl₂, 0 °C; then AcOH (excess), EtOAc-H₂O (200:1), 25 °C (75%)
2. Dibal-H, CH₂Cl₂, -90 °C



Scheme 22. Synthesis of intermediate **99**.

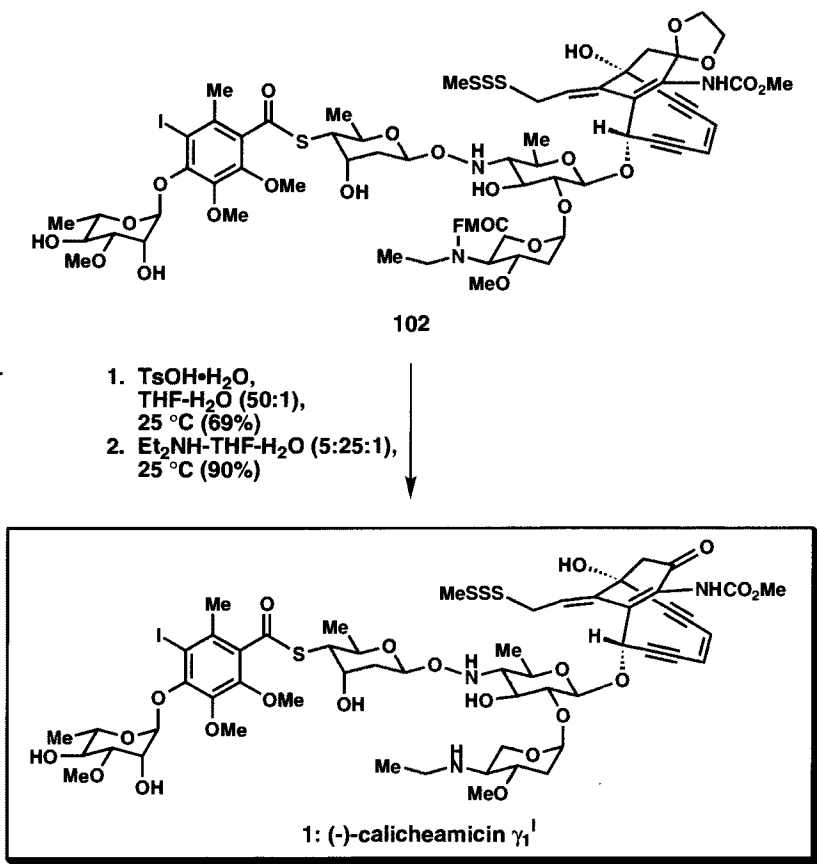
treatment of the corresponding allylic thiol with Harpp's *N*-(methylthio)phthalimide³⁸ (see **100**, Scheme 23). Subsequent studies by Danishefsky³² and by our group^{7b,e} provided additional precedent for this important transformation. Thus, reductive cleavage of the thioacetate function with Dibal-H furnishes an allylic



Scheme 23. Synthesis of intermediate **102**.

thiol (see **99**, Scheme 22), which can subsequently be converted into the desired methyl trisulfide **101** on treatment with Harpp's reagent **100** (see Scheme 23). Fortunately, it is possible, at this stage, to remove impurities from compound **101** by silica gel chromatography and proceed with the synthesis with pure compound.

The completion of the total synthesis only requires a few deprotection steps. It was gratifying to find that the final deprotections could be conducted smoothly and without compromising the newly introduced and potentially labile trisulfide residue. In particular, exposure of intermediate **101** to the action of HF•pyridine results in the cleavage of all five triethylsilyl ethers, providing **102** in 90% yield (Scheme 23). Finally, hydrolytic cleavage of the ethylene ketal with aqueous *para*-toluenesulfonic acid in THF, followed by removal of the Fmoc protecting group with diethylamine furnishes calicheamicin γ_1^I (**1**) (see Scheme 24). Synthetic calicheamicin γ_1^I , produced in this manner, exhibited physical and spectroscopic properties identical to those of an authentic sample.



Scheme 24. Synthesis of (-)-calicheamicin γ_1^I (**1**).

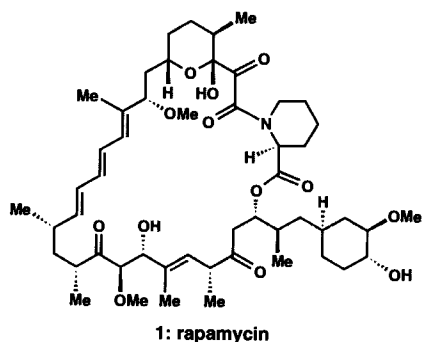
30.4 Conclusion

On the basis of chemical degradation studies and spectroscopic data, scientists at Lederle elucidated the structure of calicheamicin γ_1^I (**1**), the prototype of an unprecedented class of naturally occurring antitumor agents.¹ During the course of that landmark effort, the Lederle group also performed informative experiments that demonstrated calicheamicin's proclivity for undergoing conversion to a reactive aromatic diradical; this aggressive diradical, produced through the cascade of reactions illustrated in Scheme 1, induces double-strand cleavage of duplex DNA by abstracting hydrogen atoms from the phosphate sugar backbone, thereby causing cell death. The synthetic organic chemistry community was thus presented with a natural product whose molecular architecture is as striking and novel as its mode of action. Not surprisingly, the unique features of the calicheamicin γ_1^I molecule stimulated a flurry of research activities aimed at: (a) the development of a total synthesis of the natural product, and (b) the design and synthesis of nonnatural analogs that might also exhibit useful antitumor activity. With respect to the latter endeavor, many nonnatural enediyne-containing molecules have already been synthesized and have been found to exhibit significant DNA-cleaving properties and potential in cancer chemotherapy.^{6,39} On the other hand, progress with respect to the former endeavor has, understandably, been much slower. In addition to the total synthesis described in this chapter, the Danishefsky group has also disclosed a successful total synthesis.³⁶ It would not be fair to view these two syntheses as isolated achievements, for both have been influenced, in important ways, by the efforts and accomplishments of others in the field, and even by each other.

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K. C. Nicolaou (1993)

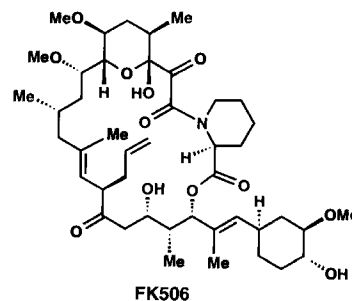
Rapamycin

31.1 Introduction

Streptomyces hygroscopicus, a bacterial species indigenous to the soil of Rapa Nui (Easter Island) in the South Pacific, produces a complex organic molecule that displays powerful immunosuppressive, antibiotic, and cytotoxic properties. Isolated in the early 1970s by Vézina and coworkers,¹ this naturally occurring substance was given the name rapamycin. Roughly three years after the initial disclosure, Findlay and coworkers deduced, on the basis of spectroscopic and X-ray crystallographic data, the constitution and stereochemistry of the rapamycin molecule (**1**).²

The aesthetic appeal and biological properties of compound **1** notwithstanding, rapamycin did not attract serious attention from the chemical and biomedical communities until the advent of the cyclosporins and FK-506, two powerful immunosuppressant drugs, in the 1980s. Rapamycin's striking resemblance to the structure of FK-506 and its potent immunosuppressive properties propelled it to the forefront of chemical, biological, and medical research as a challenging synthetic target, as a probe of immunological function, and as a potential drug candidate in organ transplant therapy.^{3,4}

The imposing structure and potential medicinal importance of rapamycin provide a strong impetus for the development of an efficient path by which a total synthesis can be achieved. At present, the chemical literature is replete with interesting synthetic studies that focus on various features of the rapamycin molecule. These undertakings provide salient testimony to the excitement that this natural product has generated. Rapamycin has already succumbed to four distinct and instructive total syntheses;⁵⁻⁸ this chapter will



address the efforts that culminated in the first total synthesis of this natural product by the Nicolaou group.⁵

A distinguishing feature of the Nicolaou synthesis of rapamycin is the use of a palladium-mediated tandem inter-/intramolecular Stille coupling to construct rapamycin's 31-membered macrolide ring and conjugated triene moiety. This maneuver was unprecedented in the macrolide field,⁹ and it can be applied to a fully deprotected seco substrate (*vide infra*).

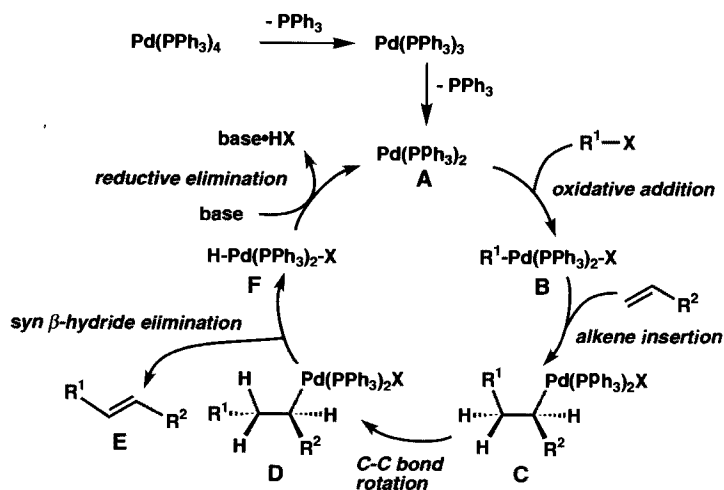
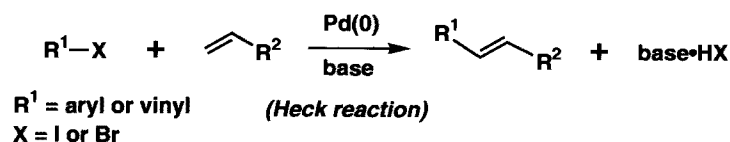
In recent years, dramatic advances in organic synthesis have accrued from developments in organotransition metal chemistry.¹⁰ Although many transition metals have provided fertile ground for the development of chemo-, regio-, and stereoselective transformations, various complexes of the Group 10 transition metal, palladium, are among the most valuable. Indeed, palladium complexes can catalyze a number of selective transformations that would either be difficult or impossible by conventional methodologies. Even after a casual survey of the current chemical literature, one is left with the impression that the already important role of palladium in organic synthesis is expanding even further. In view of the increasing importance of palladium in organic synthesis, we will, at this juncture, digress from the main subject of this chapter and discuss some of the more useful palladium-mediated carbon-carbon bond forming reactions. Our treatment of this copious and rapidly developing field is intended to be illustrative rather than comprehensive, and we sincerely apologize beforehand to those whose work has not been included. In the sections below, we address the following reactions in which palladium plays a central role: the Heck reaction, palladium-catalyzed cycloisomerizations, the Sonogashira reaction, the Suzuki reaction, and the Stille reaction.

31.1.1 The Heck Reaction

The palladium-catalyzed arylation or alkenylation of alkenes is a process known as the Heck reaction (see Scheme 1). This reaction, discovered in the late 1960s by R. F. Heck,¹¹ received scant attention in the ensuing decade, but has experienced a renaissance in the late 1980s.¹² Using only a catalytic amount of a palladium(0) complex, the Heck reaction can bring about unprecedented structural changes, particularly when conducted intramolecularly. By virtue of the achievements recorded thus far, it would appear that the Heck reaction is ideally suited for the construction of exceedingly complex molecular frameworks, often in a single step, from comparatively simple polyunsaturated precursors. The utility of this process for the efficient construction of quaternary stereogenic centers has also been demonstrated.¹³ Although the potential of this palladium-mediated process has barely been tapped, it would be fair to say, even at this early stage, that the Heck reaction is one of the true "power tools" of contemporary organic synthesis.

The current belief regarding the sequence of events involved in the Heck reaction is summarized in Scheme 1. A coordinatively unsaturated 14-electron palladium(0) complex (A) is believed to be the catalytically active species. Once formed, bis(triphenylphosphine)palladium(0) (A) initiates the first step in the catalytic cycle by taking part in an oxidative addition reaction with an alkenyl halide or an aryl halide (R^1X) to give the 16-electron complex B. Although intermediate B possesses an available coordination site which could be occupied by an olefin, it is possible that loss of a neutral donor phosphine ligand from B precedes the olefin coordination step. In any event, olefin complexation is followed by an insertion of the olefin into the σ -alkenyl or σ -aryl C-Pd bond, generating intermediate C via a four-center transition state. It is noteworthy that the crucial olefin insertion step occurs as a *syn* addition and that the organic ligand from the palladium complex becomes bonded to the less hindered carbon of the olefin; the regiochemistry of the olefin insertion is determined primarily by steric effects.

From intermediate C, the next step in the catalytic cycle involves a simple bond rotation to give D. This event is essential because it establishes the necessary *syn* relationship between a β -hydrogen and the palladium atom. With a β -hydrogen and the transition metal



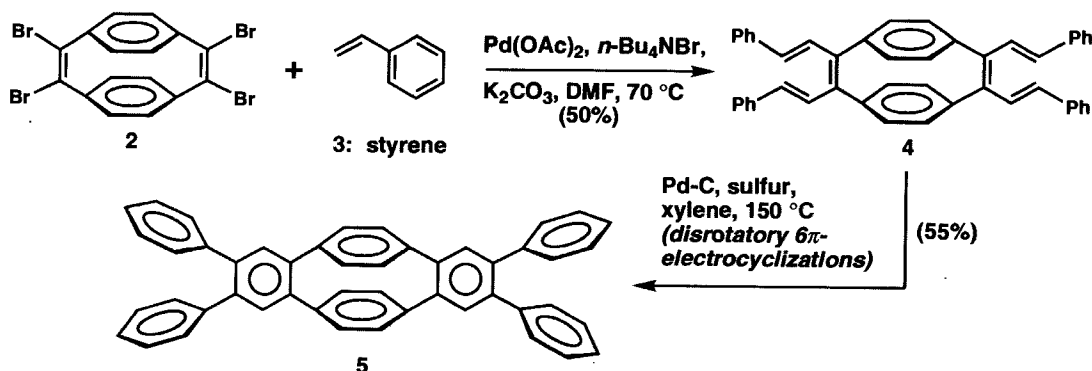
Scheme 1. Catalytic cycle for the Heck reaction.

in a common plane, the reaction-terminating β -hydride elimination can take place to give the coupling product E and the hydridopalladium complex F. Finally, a base-assisted reductive elimination of HX from the latter regenerates the palladium(0) catalyst, thus permitting a subsequent turn through the cycle. It is important to note that R^1 in complex B (see Scheme 1) must not contain any sp^3 -bonded hydrogen atoms at the β -position, otherwise a premature β -hydride elimination can compete with the desired coupling reaction.

An important virtue of the Heck reaction is that it can be applied with much success to essentially every type of olefin, although electron-deficient olefins are particularly well-suited. Moreover, the Heck reaction tolerates a variety of functional groups, and often does not require rigorous exclusion of oxygen and water.^{11b} In fact, many alkene arylations proceed very efficiently in water.¹⁴

To illustrate the utility of the Heck reaction in organic synthesis, we will address a few of the many spectacular achievements reported thus far. For a much more thorough treatment of this important subject, we direct the reader's attention to a recent review by de Meijere and Meyer.^{12a}

In 1987, de Meijere et al. reported that a modified Heck reaction can be used to effect an impressive multicomponent coupling of one molecule of the [2.2]-paracyclophanediene tetrabromide **2** with four molecules of styrene (**3**) (see Scheme 2).¹⁵ Under the indicated conditions, the four bromine substituents in **2** are replaced by four styryl groups through consecutive Heck couplings, affording compound **4** in 50% yield. Interestingly, when a solution of the latter compound and Pd-C in xylene is heated in the presence of air or with sulfur, two disrotatory 6π -electrocyclizations take place to give, after aromatization, the benzoannulated product **5** (55% yield). Compound **5** is a striking polyaromatic assembly that contains eight orthogonal biphenyl moieties.

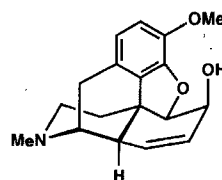


Scheme 2. de Meijere's fourfold Heck coupling-electrocyclization process.

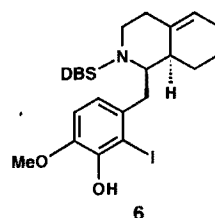
Although its potential in the realms of industrial and academic organic synthesis is just beginning to be recognized, the intramolecular Heck reaction is especially suited for the construction of congested polycyclic frameworks and quaternary stereogenic centers. This is amply demonstrated in the elegant synthetic studies of L. E. Overman and his group at UC Irvine.¹⁶ During the course of a concise synthesis of (–)-morphine (**9**) (see Scheme 3), it was found that exposure of **6** to 10 mol % of the active catalyst derived from $\text{Pd}(\text{OCOCF}_3)_2(\text{PPh}_3)_2$ and 1,2,2,6,6-pentamethylpiperidine (pempidine) in refluxing toluene results in the formation of the unsaturated morphinan **7** in 60% yield.¹⁷ A new carbocyclic ring and a crucial quaternary stereocenter are formed in this intramolecular process. After cleavage of the benzyl ether in **7**, peracid oxidation of the C–C double bond followed by *trans* diaxial opening of the oxirane ring furnishes **8**, a compound that can then be transformed into (–)-morphine (**9**) in a few straightforward steps. Interestingly, when the modified substrate **10** is subjected to a nearly identical reaction, pentacycle **12** is produced in 56% yield.^{16b} This productive transformation is initiated by an intramolecular Heck insertion to form the tetracyclic π -allylpalladium intermediate **11**; pentacycle **12**, which possesses the complete skeleton of the opium alkaloids, is then revealed after an intramolecular nucleophilic attack by the free phenolic hydroxyl group on the electrophilic π -allylpalladium moiety. From **12**, only a short sequence of modifications was required to complete the total synthesis of (–)-morphine (**9**).

A most convincing demonstration of the utility of the intramolecular Heck cyclization can be found in the racemic syntheses of the scopadulcic acid diterpenes¹⁸ by Overman et al. (see Scheme 4). Overman's concise synthesis plan reduces the formidable scopadulcic acid problem to a transitory intermediate of the general type **15**. The C–Pd bond in **15**, formed in the initial oxidative addition step, was expected to engage the proximal exocyclic C–C double bond, generating a new organopalladium intermediate after olefin insertion. The latter intermediate would then be poised for a second olefin insertion, this time with the trisubstituted cycloheptene double bond. If successful, this double Heck cyclization would accomplish the formation of rings B, C, and D of the scopadulcic acids, including the two critical quaternary stereogenic centers.

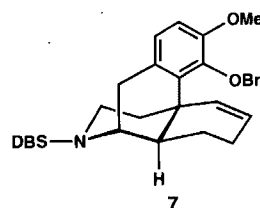
The successful implementation of this strategy is shown in Scheme 4. In the central double cyclization step, the combined action of palladium(II) acetate (10 mol %), triphenylphosphine (20 mol %), and silver carbonate (2 equiv.) on trienyl iodide **16** in refluxing THF results in the formation of tricycle **20** (ca. 83% yield). Compound **20** is the only product formed in this spectacular transformation. It is noteworthy that the stereochemical course of the initial insertion (see **17** \rightarrow **18**) is guided by an equatorially disposed *t*-butyldimethylsilyl ether at C-6 in a transition state having a preferred eclipsed orientation of the C–Pd σ bond and the exocyclic double bond (see **17**). Insertion of the trisubstituted cycloheptene double bond into the C–Pd bond in **18** then gives a new organopal-



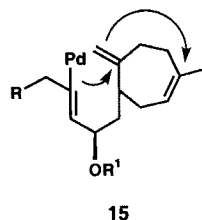
9: (–)-morphine



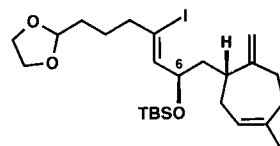
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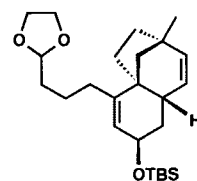
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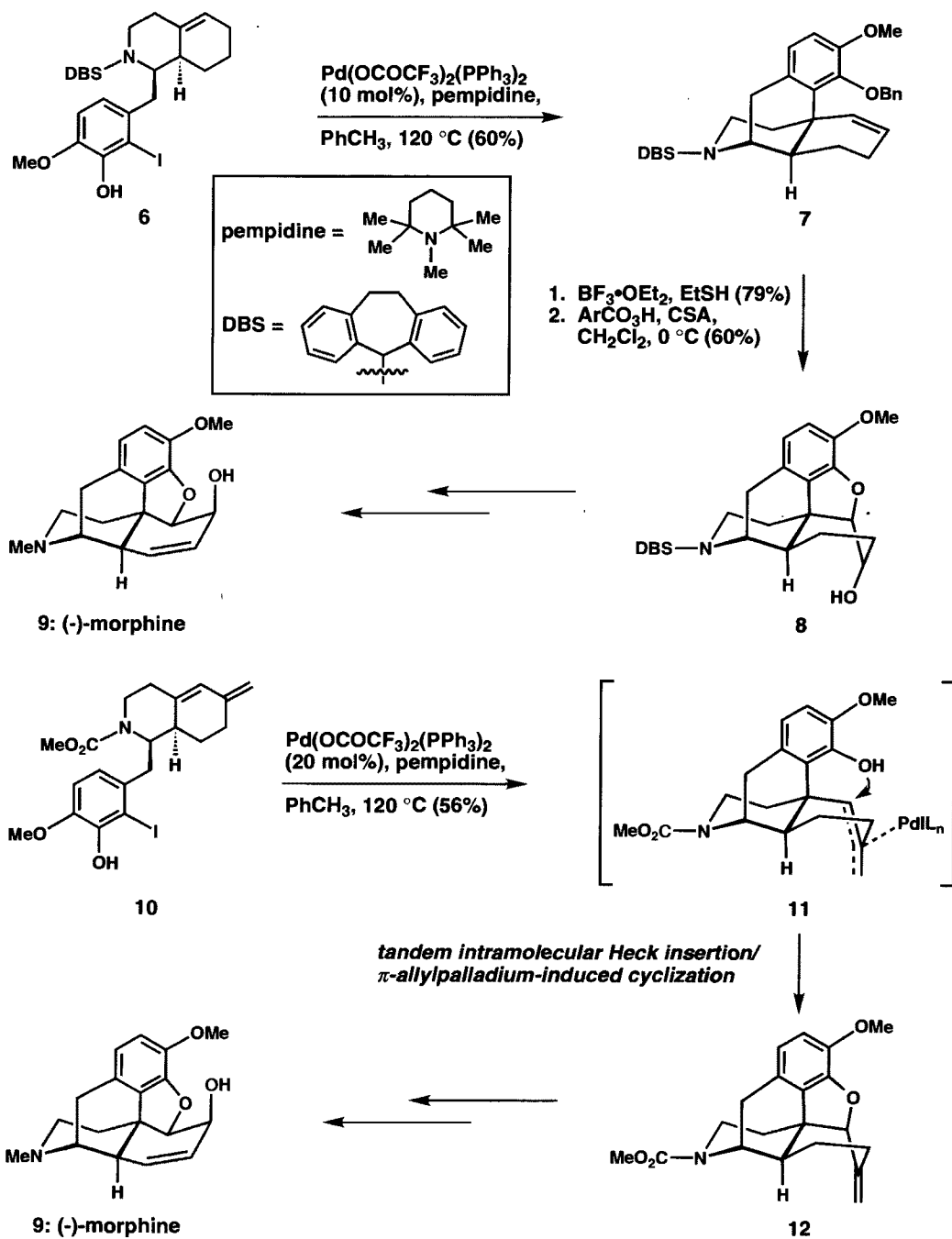
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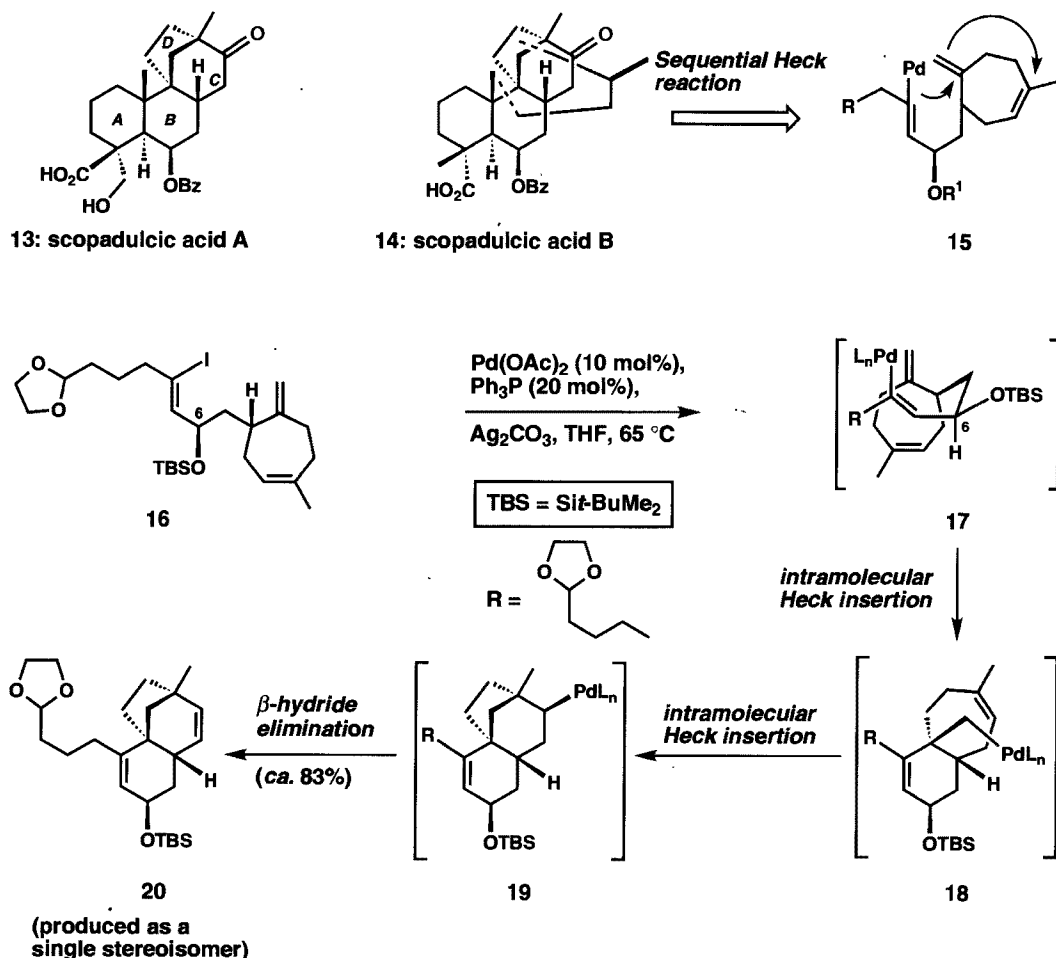
16



20



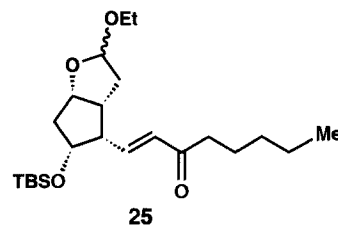
Scheme 3. Overman's intramolecular Heck strategies for the synthesis of (-)-morphine (**9**).

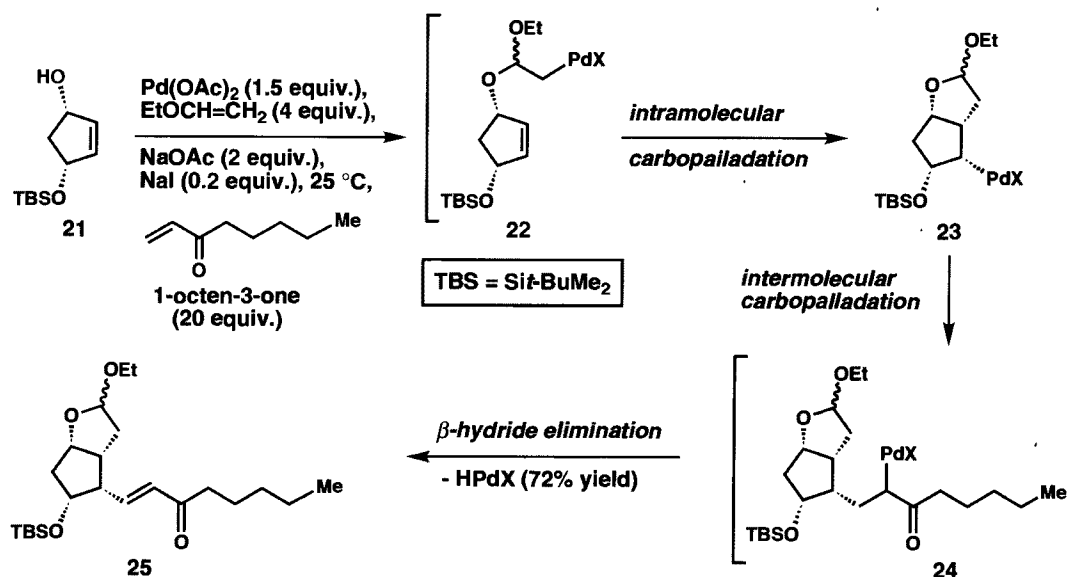


Scheme 4. Overman's sequential Heck cyclization approach to the synthesis of the scopadulcic acids.

ladium intermediate (see **19**) which undergoes conversion to tri-cycle **20** through a *syn* β -hydride elimination. By way of this strategy, multigram quantities of **20** could be procured, and the first total synthesis of (\pm)-scopadulcic acid A (**13**) could be achieved in 17 additional steps.^{18b}

Sequential Heck couplings also figure prominently in an interesting variant of the three-component coupling strategy for prostaglandin synthesis. Indeed, Larock and Lee disclosed, in 1991, an appealing synthesis of the versatile prostaglandin precursor **25** (see Scheme 5) based on a one-pot, palladium-mediated union of three alkenes.¹⁹ In the crucial trimolecular coupling event, chiral allylic alcohol **21**, ethyl vinyl ether, and 1-octen-3-one are simply combined in the presence of Pd(OAc)_2 , NaOAc, and a catalytic amount

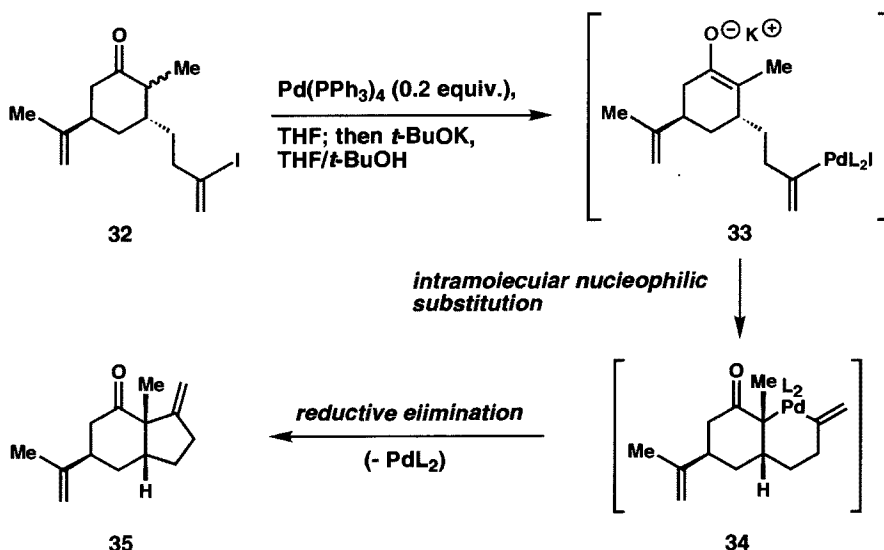




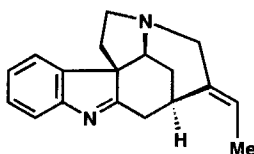
Scheme 5. Larock's palladium-promoted, three-component coupling strategy for prostaglandin synthesis.

of NaI. After approximately three hours at 25 °C, bicyclic enone **25** is produced in 72 % yield as a mixture of acetal stereoisomers. This elegant, one-pot transformation commences with a palladium(II)-induced oxypalladation of the electron-rich ethyl vinyl ether to give organopalladium intermediate **22**. The latter can then undergo isomerization to **23** through an intramolecular Heck insertion. It is instructive to note that **23** cannot undergo an undesirable *syn* β -hydride elimination because there is no hydrogen atom with a *syn* orientation with respect to the metal center. Intermediate **23** is thus available for an intermolecular Heck coupling with 1-octen-3-one, an event which gives organopalladium intermediate **24**. A β -hydride elimination completes the construction of bicyclic enone **25**.

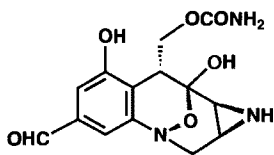
Although the terminating *syn* β -hydride elimination step in the Heck reaction is ordinarily a rather facile process, intramolecular Heck insertions may compete successfully with β -elimination in some settings. Oppolzer's palladium-catalyzed tricyclization process is an impressive and elegant example²⁰ (see Scheme 6). In the event, subjection of monocycle **26** to the indicated conditions presumably affords a transient π -allylpalladium intermediate **27** which undergoes conversion to σ -alkylpalladium intermediate **28** through a suprafacial palladium–ene cyclization. Intramolecular Heck insertion of the coordinated alkene in **28** into the C–Pd bond, with retention of configuration, closes ring C and gives a new σ -alkylpalladium intermediate (**29**). Although the cyclization cascade could be terminated at this stage through a β -hydride elimina-



Scheme 7. Piers's palladium-catalyzed methylenecyclopentane annulation method.



(±)-**40**: (±)-dehydrotubifoline

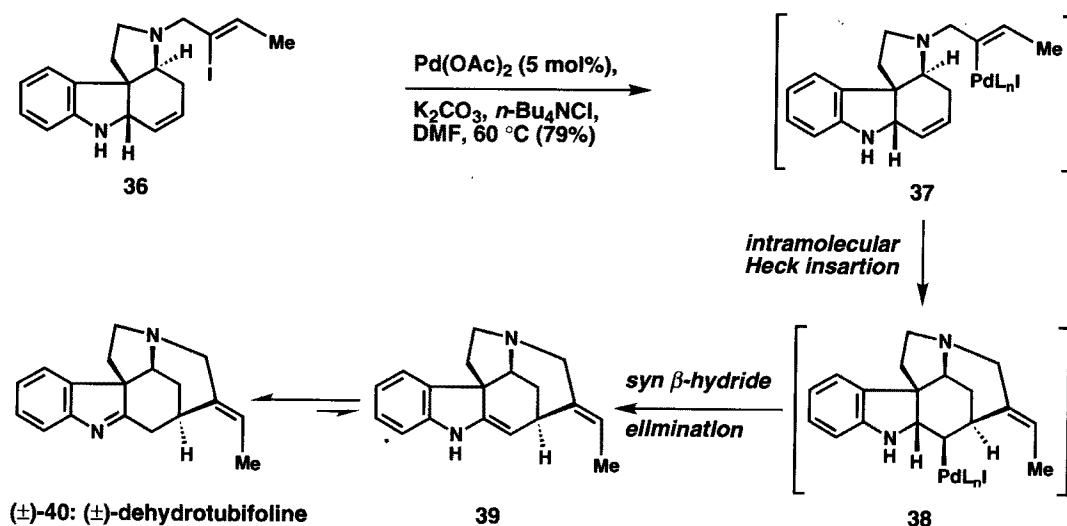


(±)-**43**: (±)-FR-900482

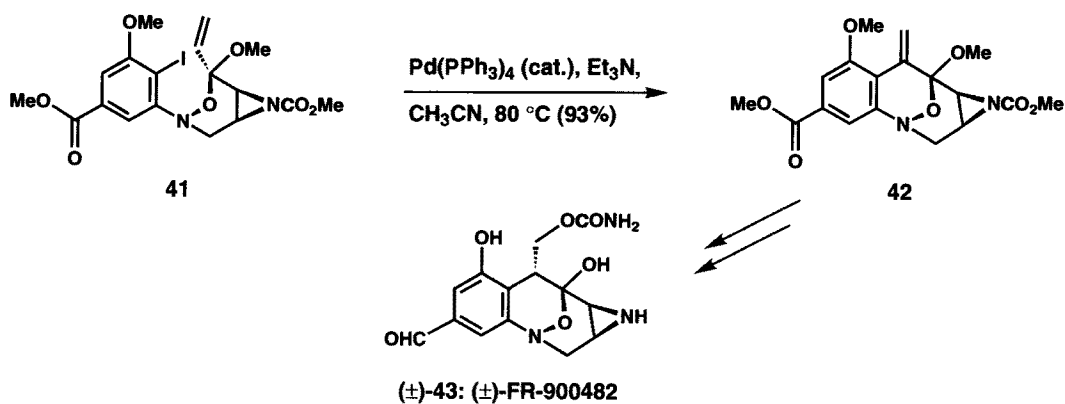
sion to the six-membered palladacycle **34** through intramolecular nucleophilic substitution. Bicyclic **35** is then produced after a simple reductive elimination.

The intramolecular Heck reaction presented in Scheme 8 is also interesting and worthy of comment. Rawal's potentially general strategy for the stereocontrolled synthesis of the *Strychnos* alkaloids is predicated on the palladium-mediated intramolecular Heck reaction. In a concise synthesis of (±)-dehydrotubifoline [(±)-**40**],²² Rawal et al. accomplished the conversion of compound **36** to the natural product under the conditions of Jeffery.²³ In this ring-forming reaction, the σ -alkenylpalladium(II) complex formed in the initial oxidative addition step engages the proximate cyclohexene double bond in a Heck cyclization, affording enamine **39** after *syn* β -hydride elimination. The latter substance is a participant in a tautomeric equilibrium with imine (±)-**40**, which happens to be shifted substantially in favor of (±)-**40**.

During the course of an elegant synthesis of the multifunctional FR-900482 molecule [(±)-**43**, Scheme 9], the Danishefsky group accomplished the assembly of tetracycle **42** using an intramolecular Heck arylation as a key step.²⁴ In the crucial C–C bond forming reaction, exposure of aryl iodide **41** to a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine in acetonitrile at 80 °C effects the desired Heck arylation, affording **42** in an excellent yield of 93 %. The impressive success of this cyclization reaction is noteworthy in view of the potentially sensitive functionality contained within **41**.



Scheme 8. Rawal's Heck cyclization strategy for the synthesis of (±)-dehydrotubifoline [(±)-40].

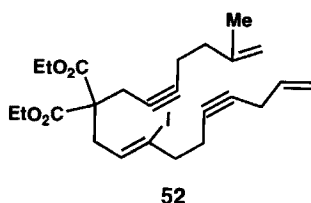
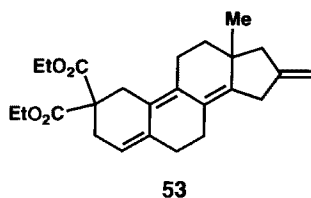


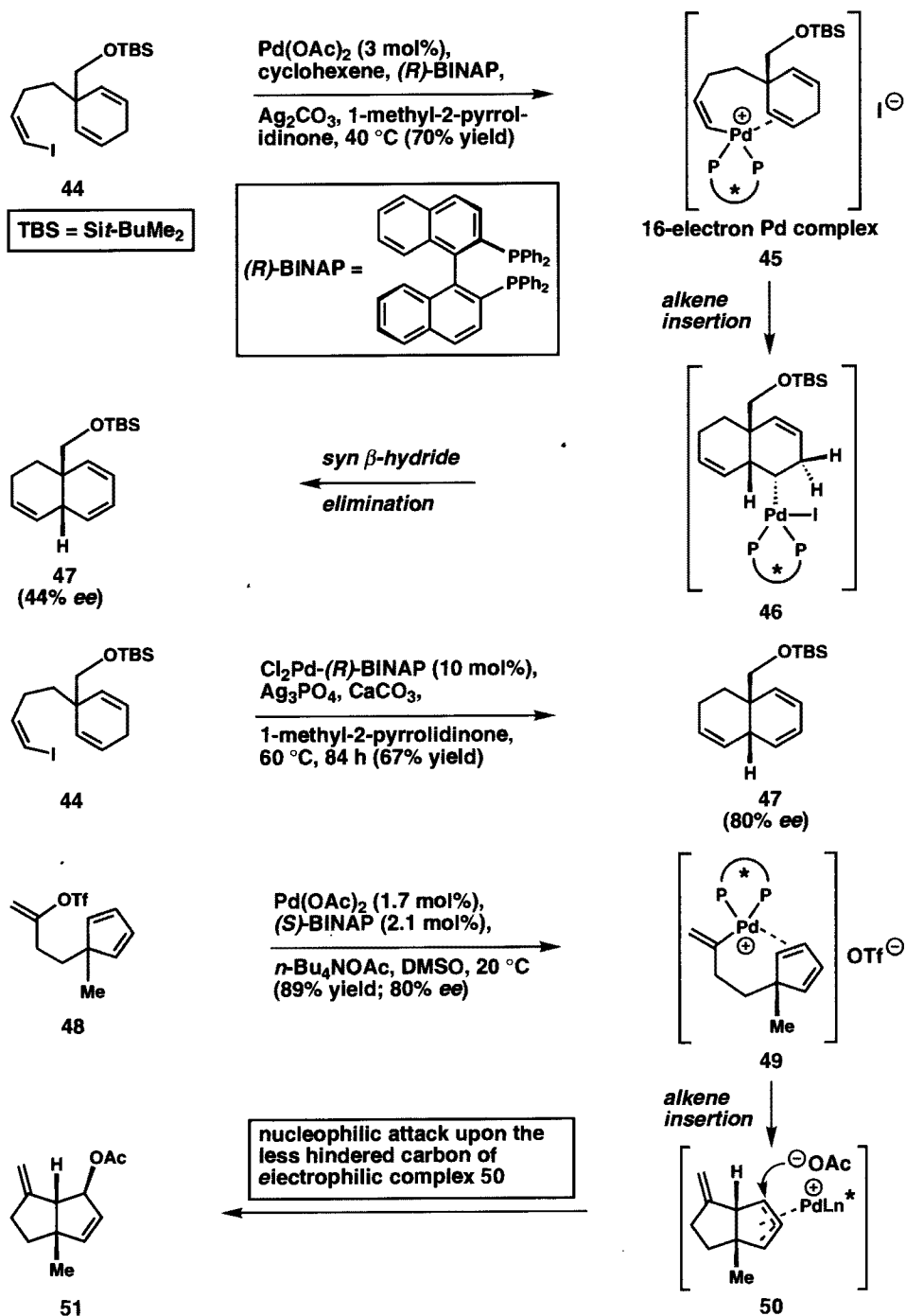
Scheme 9. Danishefsky's intramolecular Heck arylation approach to the synthesis of (±)-FR-900482 [(±)-43].

Interestingly, the asymmetric palladium(0) catalyst generated *in situ* from $\text{Pd}(\text{OAc})_2$, cyclohexene, and (*R*)-BINAP can accomplish an enantiotopic group selective Heck cyclization of the prochiral monocyclic compound **44** (see **44** \rightarrow **47**, Scheme 10). This exciting transformation, disclosed by Shibasaki and his group in Japan,²⁵ represents the first application of the Heck reaction to catalytic asymmetric synthesis. Under the indicated conditions, prochiral vinyl iodide **44** is converted to the *cis*-decalin derivative **47** in 70% yield and with 44% enantiomeric excess (*ee*). The silver salt is an essential additive that presumably induces the formation of the 16-electron Pd^+ complex **45**; the ability of the metal center to discriminate between the two enantiotopic double bonds is a function of the asymmetric environment created by the bidentate (*R*)-BINAP ligand. In the absence of a silver salt, the iodide remains attached to the metal center and partial dissociation of the optically active bidentate ligand occurs, thereby lowering the enantioselectivity of the overall process. In the progression from **45** to the final product, it is presumed that insertion of the coordinated alkene in **45** into the C–Pd bond takes place to give intermediate **46**. Finally, a terminating *syn* β -hydride elimination affords *cis*-decalin derivative **47**, and a base-induced reductive elimination of HI returns the asymmetric palladium(0) catalyst to the reaction. It is noteworthy that subsequent to the initial disclosure, Shibasaki *et al.* reported that the action of $\text{Cl}_2\text{Pd}-(R)\text{-BINAP}$ (10 mol %), Ag_3PO_4 (2 equiv.), and CaCO_3 (2.2 equiv.) in 1-methyl-2-pyrrolidinone at 60°C on the same prochiral vinyl iodide **44** can bring about the formation of *cis*-decalin derivative **47** in an improved 80% *ee* (see Scheme 10).^{25b}

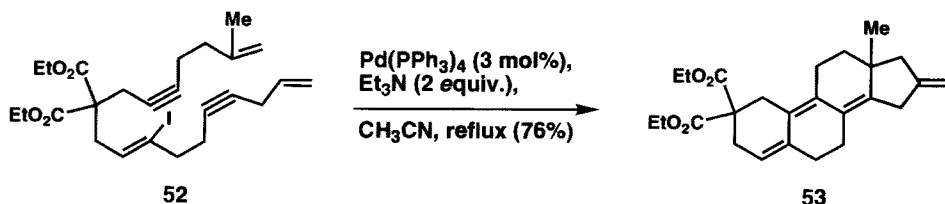
In an extension of this work, the Shibasaki group developed the novel transformation **48** \rightarrow **51** shown in Scheme 10.^{25c} To rationalize this interesting structural change, it was proposed that oxidative addition of the vinyl triflate moiety in **48** to an asymmetric palladium(0) catalyst generated under the indicated conditions affords the 16-electron Pd^+ complex **49**. Since the weakly bound triflate ligand can easily dissociate from the metal center, a silver salt is not needed. Insertion of the coordinated alkene into the vinyl C–Pd bond then affords a transitory π -allylpalladium complex **50** which is captured in a regio- and stereocontrolled fashion by acetate ion to give the optically active bicyclic diene **51** in 80% *ee* (89% yield). This catalytic asymmetric synthesis by a Heck cyclization/anion capture process is the first of its kind.

Any discussion of the Heck reaction in organic synthesis would be incomplete without mention of the elegant contributions of E. Negishi and his group at Purdue.^{20d,26} One particularly striking contribution is presented in Scheme 11. Compound **53** possesses a tetracyclic carbon skeleton characteristic of the steroids, and it can be constructed in a single operation from the polyunsaturated acyclic molecule **52** using a “domino” Heck cyclization strategy.²⁶ In the event, an oxidative addition of the C–I bond in **52** to a palladium(0) complex initiates a cascade of cyclic carbopalladations ul-





Scheme 10. Shibasaki's asymmetric Heck cyclization process.



Scheme 11. Negishi's palladium-catalyzed "zipper" tetracyclization process.

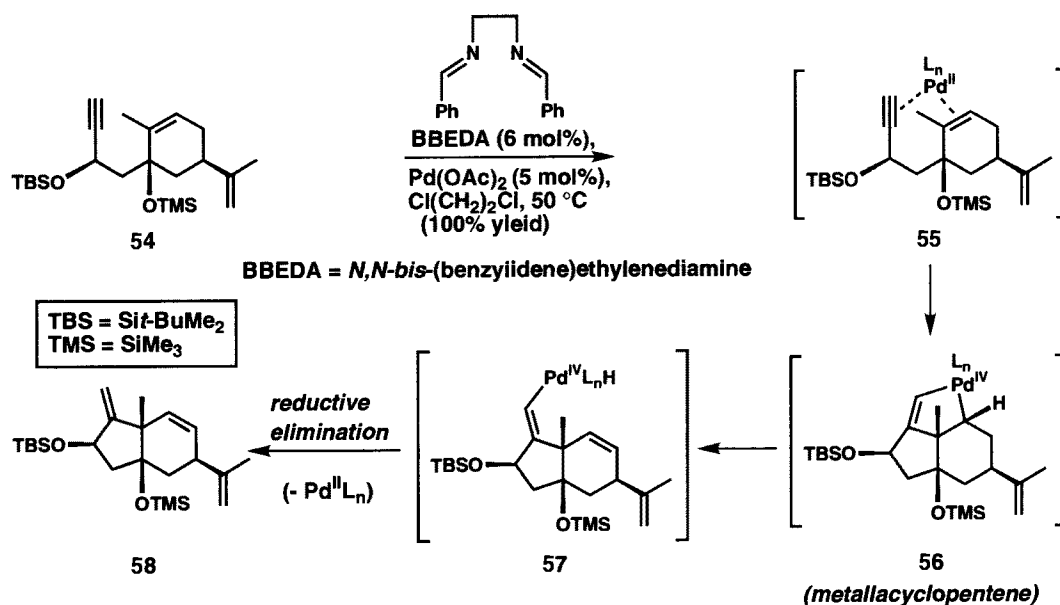
mately affording **53**; four new C–C bonds and four carbocyclic rings are created in this impressive "zipper" polycyclization process.

31.1.2 Palladium-Catalyzed Cycloisomerizations

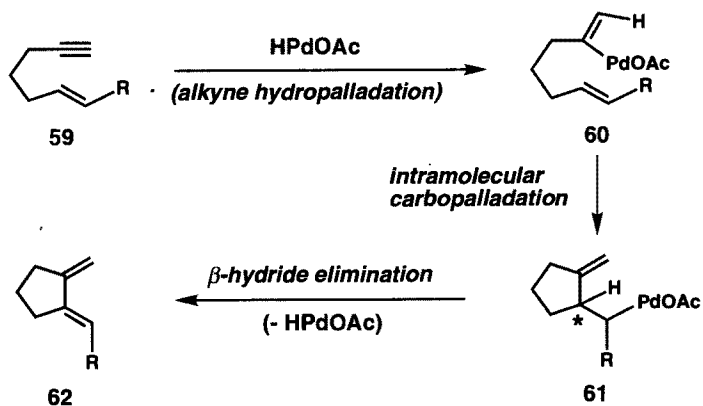
The discovery that suitably constituted polyunsaturated molecules can undergo mono- or polycyclizations in the presence of a catalytic amount of a palladium complex is among the most exciting developments in contemporary organic synthesis. Palladium-catalyzed cycloisomerizations are simple additions, and are highly atom economical because all of the atoms in the starting material are expressed in the product.²⁷ The growing popularity of such reactions is due, in large part, to their simplicity and to the dramatic increases in molecular complexity that typically attend their employment.

B. M. Trost and his group at Stanford stand foremost among the discoverers and developers of this emerging technology. In an early contribution, Trost and Jebaratnam reported the efficient palladium-catalyzed Alder ene reaction shown in Scheme 12.²⁸ This transformation features the simultaneous construction of a five-membered ring and a quaternary stereogenic center and can be brought about simply by exposing a solution of compound **54** in 1,2-dichloroethane to palladium(II) acetate (5 mol %) and *N,N*-bis(benzylidene)ethylenediamine (6 mol %) and heating the resulting mixture to 50 °C. Under these conditions, bicycle **58** is produced in 100 % yield, presumably via the organopalladium intermediates shown (see **55** → **56** → **57**, Scheme 12). It is noteworthy that bicycle **58** has much in common with the picrotaxane terpenes, and that all attempts to induce the Alder ene cyclization of **54** thermally were unsuccessful.

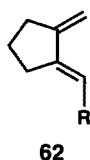
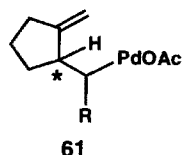
Another useful class of palladium-catalyzed cycloisomerizations is based on the general mechanistic pathway shown in Scheme 13. In this chemistry, a hydridopalladium acetate complex is regarded as the catalytically active species.^{27b,29} According to this pathway, coordination of a generic enyne such as **59** to the palladium metal center facilitates a hydropalladation reaction to give intermediate **60**. With a pendant alkene, **60** can then participate in a ring-form-



Scheme 12. Trost's palladium(II)-catalyzed Alder ene cyclization process.



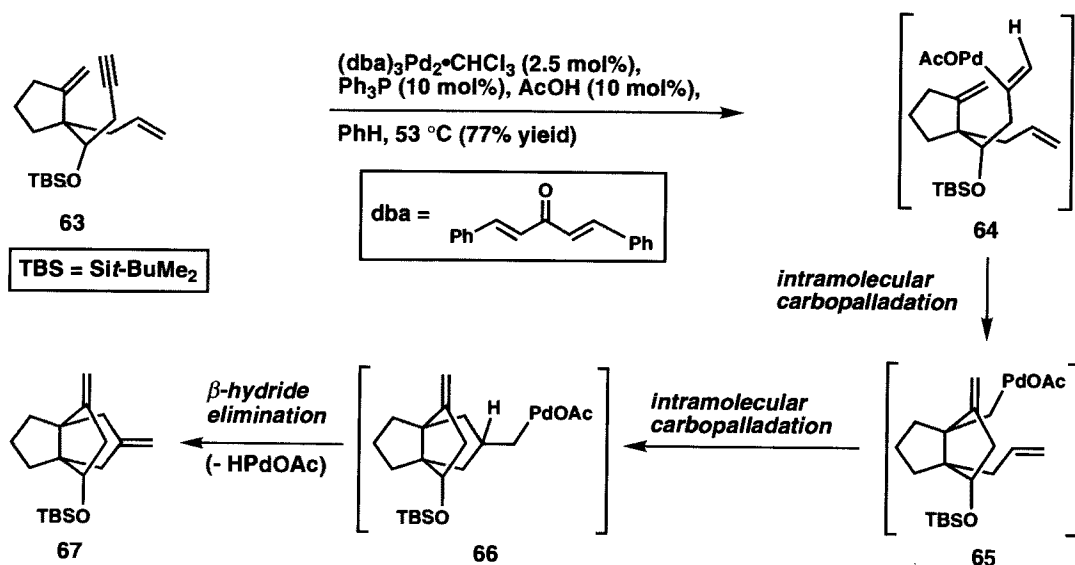
Scheme 13. Trost's hydridopalladium acetate catalyzed cycloisomerization chemistry.



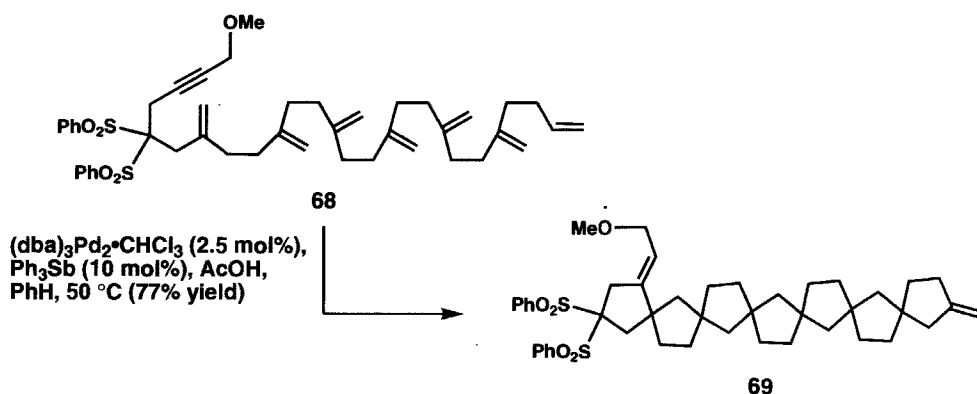
ing carbopalladation to give **61**. The hydrogen atom attached to C* in the latter intermediate is important because it permits a β -hydride elimination, which generates a potentially valuable 1,3-diene (see **62**) and regenerates the hydridopalladium acetate catalyst.

A careful analysis of the catalytic cycle described above engenders the idea that if the terminating β -hydride elimination step (see **61** \rightarrow **62**) can be avoided, or at least suppressed, then organopalladium intermediate **61** could, in principle, initiate further cyclizations.^{27b} Indeed, dienyne **63** can be converted in one step to [3.3.3]propellane **67** under the conditions given in Scheme 14 (77% yield).³⁰ It is presumed that hydridopalladium acetate (HPdOAc), generated *in situ* through oxidative addition of AcOH to the palladium(0) complex, reacts with **63** to give **64**. [3.3.3]Propellane **67** is then formed after sequential carbopalladations and a terminating β -hydride elimination (see **64** \rightarrow **65** \rightarrow **66** \rightarrow **67**). It is instructive to note that bicyclic organopalladium intermediate **65** cannot take part in an undesirable β -hydride elimination.

Although the conversion of **63** \rightarrow **67** adequately expresses the utility of palladium-catalyzed cycloisomerizations for the construction of complex polycycles, the single-step, palladium-mediated conversion of compound **68** to the novel polyspirocycle **69**^{30,31} (Scheme 15) can perhaps be regarded as the paragon of this chemistry. In this striking transformation, chemo- and regioselective



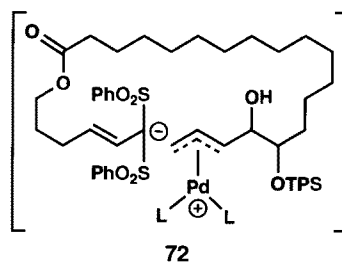
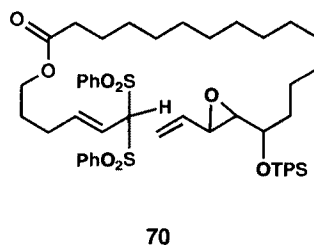
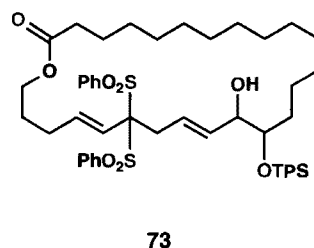
Scheme 14. Trost's approach to [3.3.3]propellane **67** by hydridopalladium acetate-catalyzed sequential cycloisomerization.

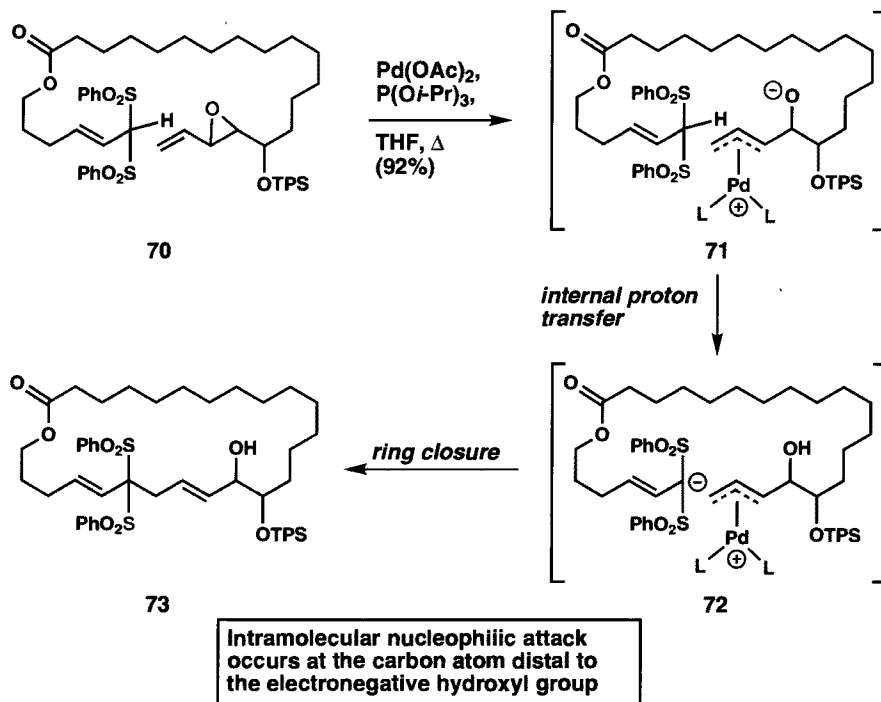


Scheme 15. Trost's hydridopalladium acetate-catalyzed "zipper" polycyclization.

hydropalladation of the alkyne function in **68** is the first event in a polycyclization cascade that results in the formation of seven carbocyclic rings! In palladium-catalyzed "zipper" reactions such as this one, the nature of the polycycle formed depends only on the arrangement of the various sites of unsaturation in the acyclic precursor.

Palladium complexes can also induce macrocyclizations.³² For example, compound **73**, a 26-membered macrolide, can be produced in an excellent yield of 92 % upon treatment of vinyl epoxide **70** with triisopropylphosphite and palladium(II) acetate (see Scheme 16).³³ In this efficient transformation, palladium(0), which forms *in situ* through reduction of palladium(II) acetate with triisopropylphosphite, reacts with vinyl epoxide **70** to give intermediate **71**; the latter is interesting because it possesses an electrophilic π -allylpalladium complex and a basic alkoxide ion. For the desired cyclization to occur, the carbon bearing the two anion-stabilizing sulfone moieties must be deprotonated. This prerequisite could be fulfilled if this terminal carbon and the basic alkoxide ion can be brought into proximity, thereby allowing the desired proton transfer. An interesting consequence of an internal proton transfer such as this (see **71** \rightarrow **72**, Scheme 16) is that the newly formed carbanion finds itself in proximity to the electrophilic π -allylpalladium complex (see **72**). In a nonpolar reaction medium, charge–charge attraction prevents the nucleophile and electrophile from diffusing away from each other; the desired macrocyclization is thus driven by charge neutralization.

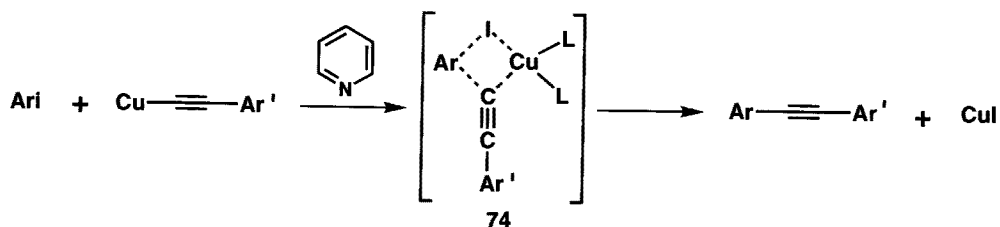




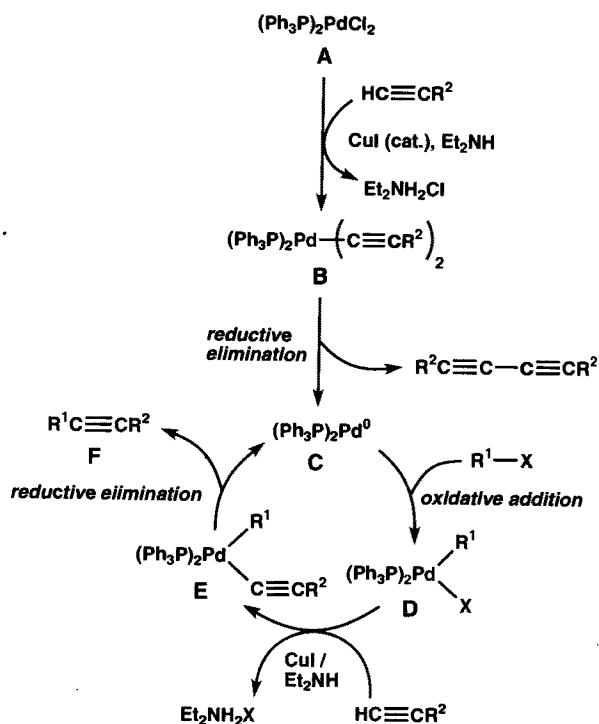
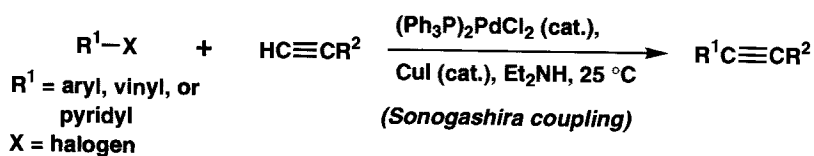
Scheme 16. Trost's palladium-mediated macrocyclization process.

31.1.3 The Stephens–Castro and the Sonogashira Couplings

In 1963, Stephens and Castro disclosed the interesting observation summarized in Scheme 17. They found that diarylacetylenes can be produced in good yield upon treatment of aryl iodides with copper(I) acetylides in refluxing pyridine.³⁴ To rationalize this potentially valuable metathesis reaction, a concerted path via a four-center transition state of the type **74** was proposed. Soon after this discovery, it was shown that iodoalkenes are also suitable coupling partners in this type of transformation.³⁵ Considering the obvious utility of a process that forms a bond between sp - and sp^2 -hybridized carbon atoms, the impetus for finding milder reaction conditions for such a coupling was significant. Roughly twelve years after the pioneering report by Stephens and Castro, Sonogashira and his colleagues in Japan demonstrated that terminal alkynes react smoothly with bromoalkenes, iodoarenes, and bromopyridines in the presence of catalytic amounts of bis(triphenylphosphine)palladium dichloride and cuprous iodide in diethylamine at room temperature (see Scheme 18).^{36,37} This mild process has significantly



Scheme 17. The Stephens–Castro coupling reaction.

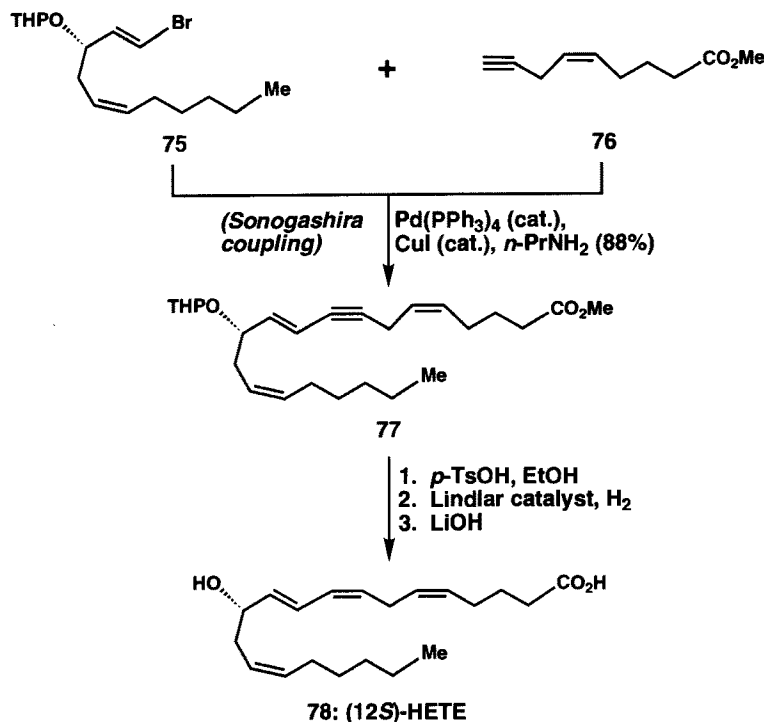


Scheme 18. Catalytic cycle for the Sonogashira coupling.

extended the utility of the Stephens–Castro-type reaction, and has performed very well in a variety of contexts in organic synthesis. In recognition of the valuable contribution of Sonogashira *et al.*, the $\text{Pd}^0/\text{Cu}^{\text{I}}$ -catalyzed coupling of sp - and sp^2 -hybridized carbon atoms is often referred to as the Sonogashira coupling reaction.

The presumed catalytic cycle for the Sonogashira coupling is shown in Scheme 18.³⁶ Bis(triphenylphosphine)palladium(0) (see C), the putative active catalyst, could conceivably be formed *in situ* through sequential copper(I) iodide-catalyzed bis-alkynylation and reductive elimination reactions (see $\text{A} \rightarrow \text{B} \rightarrow \text{C}$, Scheme 18). Once formed, the highly coordinatively unsaturated 14-electron palladium(0) complex C participates in an oxidative addition reaction with the aryl or vinyl halide to give the 16-electron palladium(II) complex D. A copper(I)-catalyzed alkynylation of D then furnishes an aryl- or vinylalkynyl palladium(II) complex E. Finally, a terminating reductive elimination step reveals the coupling product (F) and regenerates the active palladium(0) catalyst.

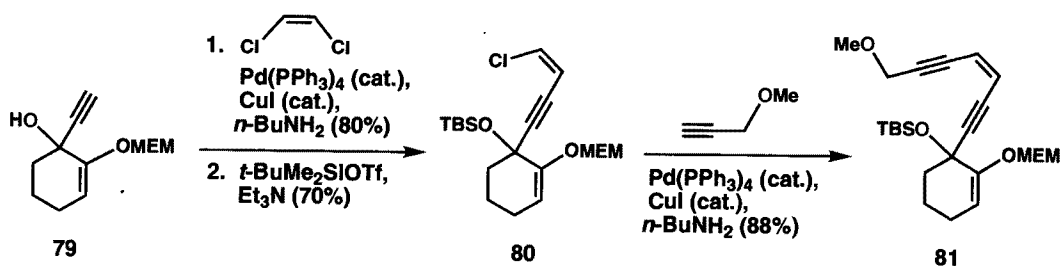
Because the Sonogashira coupling process outlined in Scheme 18 is initiated by the *in situ* reduction of palladium(II) to palladium(0), it would be expected that palladium(0) catalysts could be utilized directly. Indeed, a catalytic amount of tetrakis(triphenylphosphine)-



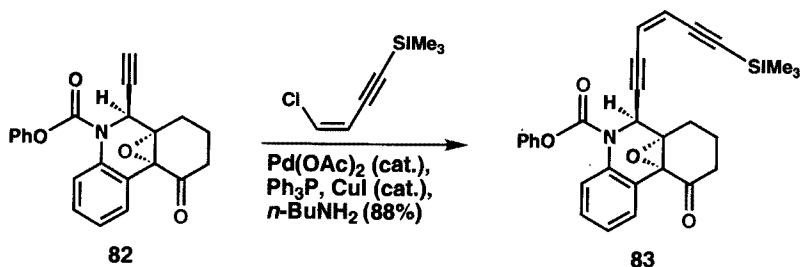
Scheme 19. The Sonogashira coupling in Nicolaou's synthesis of (12S)-HETE (78).

palladium(0) is frequently used with much success in Sonogashira couplings. It should also be noted that $\text{Pd}^0/\text{Cu}^{\text{I}}$ -catalyzed couplings of configurationally defined vinyl halides with terminal alkynes are stereospecific, proceeding with retention of alkene stereochemistry. For example, during the course of a convergent synthesis of (12*S*)-hydroxyeicosatetraenoic acid (12*S*)-HETE (**78**) (see Scheme 19), Nicolaou et al. demonstrated that (*E*)-vinyl bromide **75** and terminal alkyne **76** can be joined efficiently and stereospecifically by means of a Sonogashira coupling.³⁸ Trienyne **77**, the only coupling product observed, can be converted to **78** by a straightforward three-step reaction sequence that includes a chemo- and stereoselective Lindlar hydrogenation of the alkyne function.

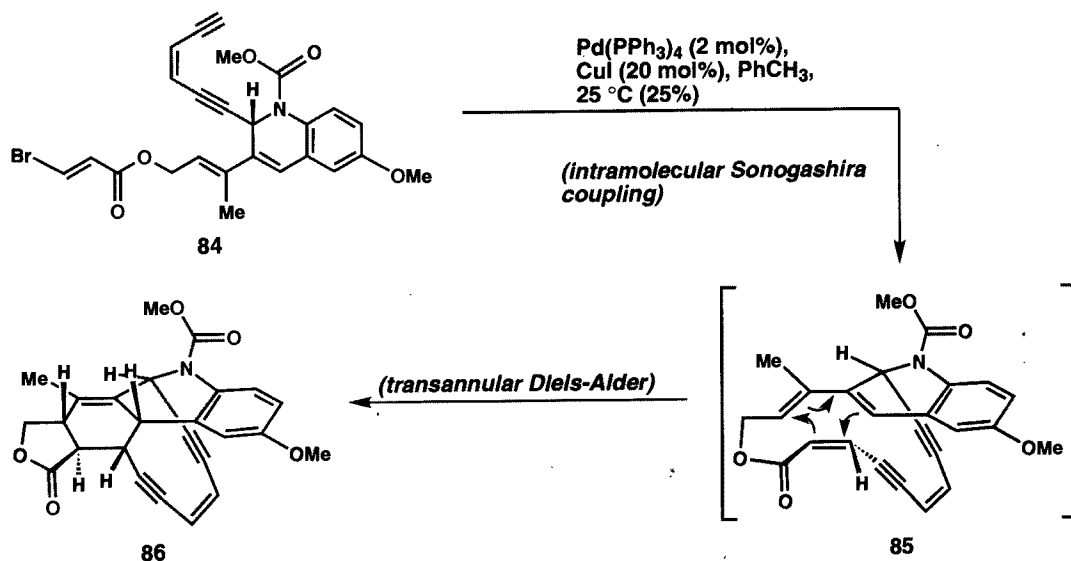
In organic synthesis, the Sonogashira coupling reaction is particularly valuable as a method for the construction of the 1,5-diyne-3-ene moiety, the characteristic structural feature of the enediyne anticancer antibiotics.³⁹ In an early contribution by Magnus et al.,⁴⁰ two Sonogashira couplings were used to construct compound **81** (see Scheme 20), a key intermediate in a synthesis of a model system related to calicheamicin and esperamicin (see **79** → **80** → **81**, Scheme 20). A Sonogashira coupling also figured prominently in a synthesis of a model system of dynemicin A by Nicolaou et al. (see **82** → **83**, Scheme 21).⁴¹



Scheme 20. Sonogashira couplings in Magnus's calicheamicin/esperamicin model study.



Scheme 21. The Sonogashira coupling reaction in Nicolaou's dynemicin A model study.

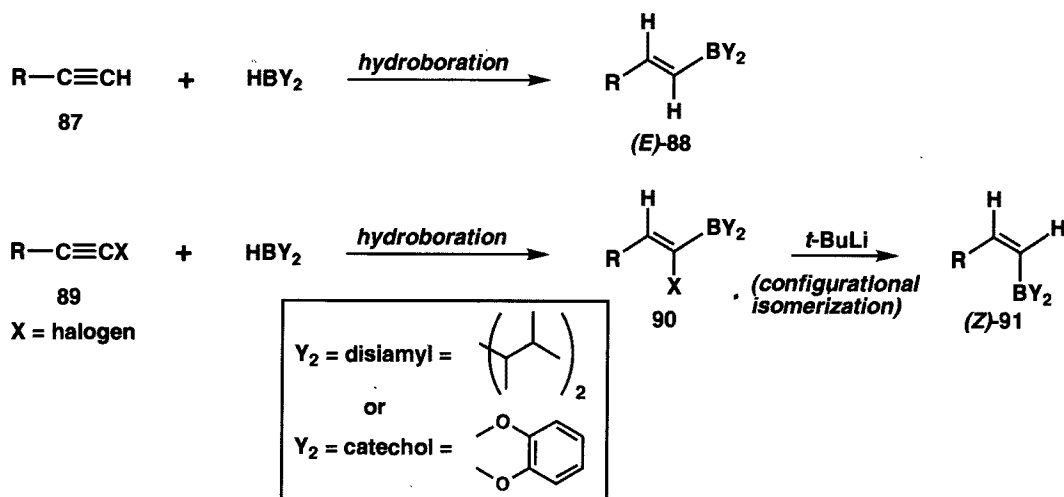


Scheme 22. Schreiber's approach to dynemicin A system **86** by a tandem Sonogashira coupling/Diels-Alder reaction.

The $\text{Pd}^0/\text{Cu}^{\text{I}}$ -catalyzed union of sp - and sp^2 -hybridized carbon atoms can also be attended by ring formation. In a recent example, Schreiber *et al.* found that subjecting **84** (see Scheme 22) to a Sonogashira reaction results in the formation of dynemicin A system **86**.⁴² In this spectacular transformation, intramolecular Sonogashira coupling of the terminal alkyne carbon with the bromine-bearing carbon in **84** affords tricycle **85** as a transitory intermediate. In **85**, the positioning of the conjugated 1,3-diene moiety and the *trans* disubstituted enoate function creates a very favorable setting for a transannular Diels-Alder reaction (see **85** \rightarrow **86**). Three rings and four contiguous stereocenters are formed in this elegant tandem Sonogashira cyclization/transannular Diels-Alder transformation.

31.1.4 The Suzuki Coupling

Another very valuable palladium-mediated coupling reaction, which bears the name of its discoverer, is the Suzuki reaction.⁴³ In organic synthesis, the Suzuki reaction is particularly useful as a method for the construction of conjugated dienes of high stereoisomeric purity, although it can accomplish other important transformations as well. Using a palladium(0) catalyst and a base such as NaOEt or NaOH , the Suzuki reaction accomplishes a cross-coupling of a 1-alkenylboron compound with an organic electrophile. This effective cross-coupling combines two facile reaction processes:

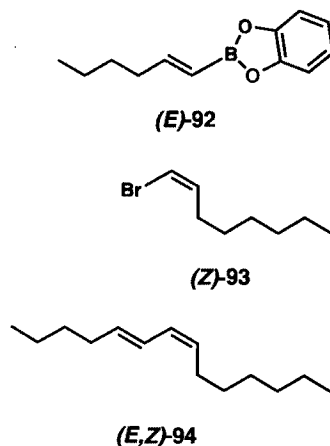


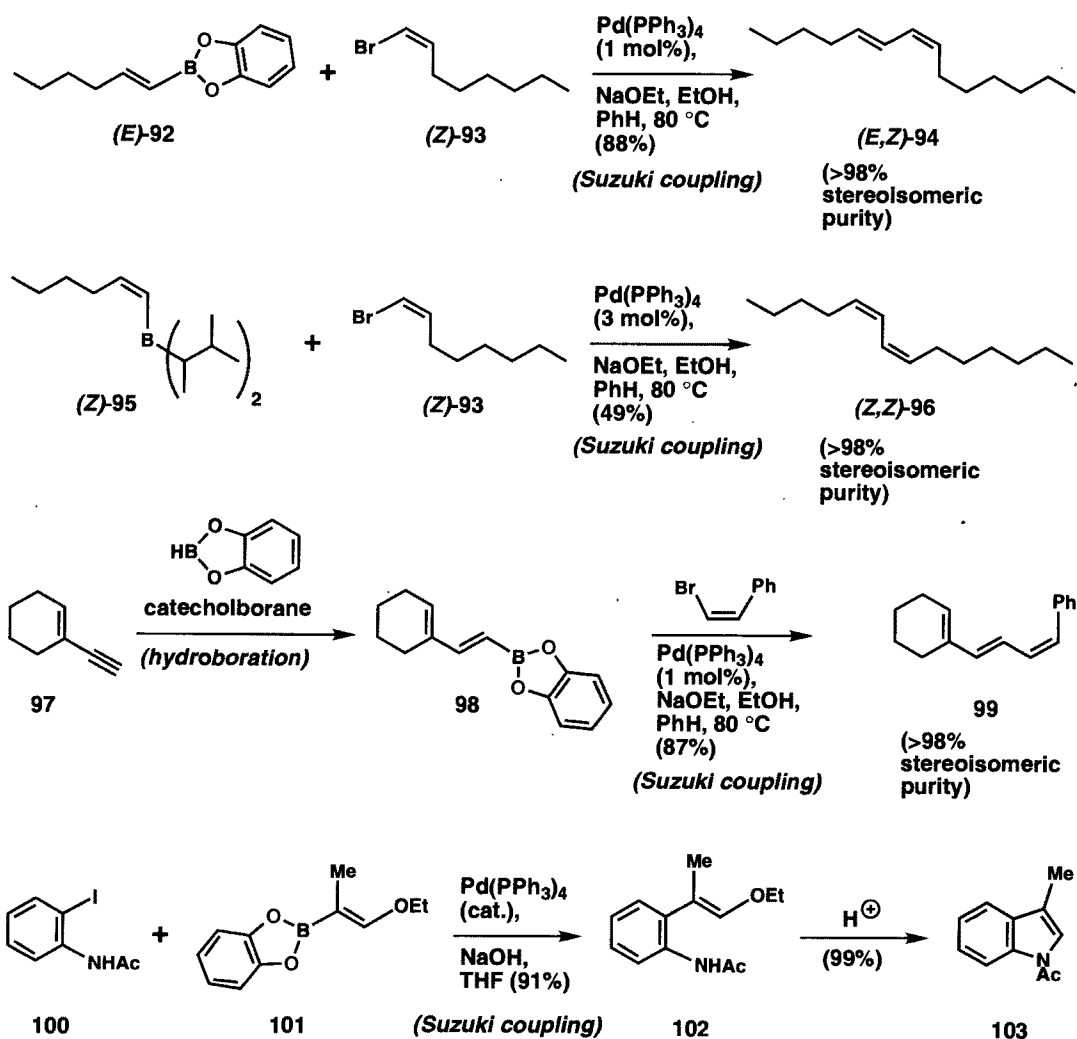
Scheme 23. Synthesis of vinyl boranes by hydroboration of alkynes.

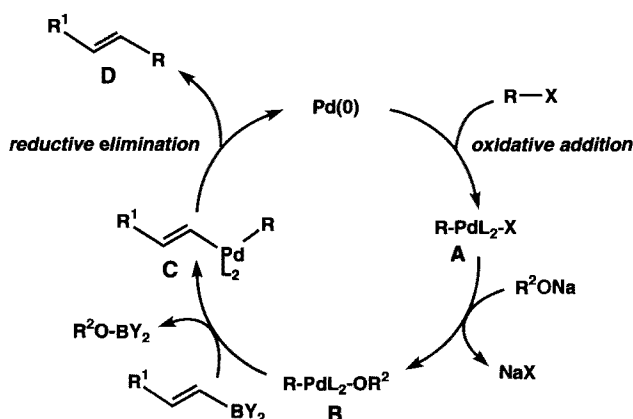
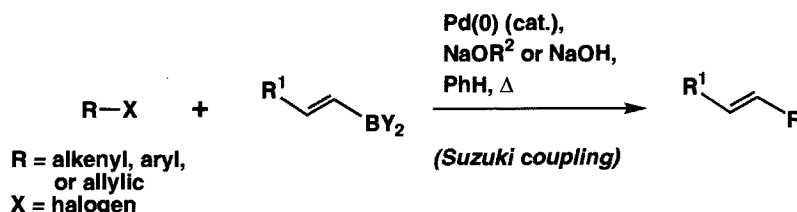
(1) the often regiospecific hydroboration of alkynes, and (2) the oxidative addition of carbon–heteroatom bonds to palladium(0). The reaction of a diorganoborane such as disiamylborane or catecholborane with a terminal alkyne of the general type **87** (see Scheme 23) provides convenient access to (*E*)-vinylboranes [see (*E*)-**88**] by a *syn* addition of the B–H bond to the alkyne. Stereoisomeric (*Z*)-vinylboranes [see (*Z*)-**91**], on the other hand, can be smoothly prepared by a two-step sequence that commences with the hydroboration of a 1-halo-1-alkyne (see **89** → **90**). The desired (*Z*)-vinylborane (**Z**)-**91** can then be formed upon exposure of the halogenated hydroboration product **90** to the action of *t*-butyllithium.

The transformations presented in Scheme 24 amply demonstrate the utility of the Suzuki coupling process for the synthesis of conjugated dienes and trienes. Stereoisomeric vinylboranes **92** and **95** combine with (*Z*)-1-octenylbromide [(*Z*)-**93**] under the indicated conditions to give (*E,Z*)-diene (*E,Z*)-**94** and (*Z,Z*)-diene (*Z,Z*)-**96** in yields of 88 and 49 %, respectively. The stereoisomeric purity of compounds (*E,Z*)-**94** and (*Z,Z*)-**96** exceeds 98 %. In an analogous manner, compound **98**, derived in one step through hydroboration of 1-cyclohexenylethyne (**97**) with catecholborane, can be joined with (*Z*)- β -styryl bromide to give triene **99**, also of greater than 98 % stereoisomeric purity (87 % yield). It is noteworthy that in each of these palladium-catalyzed alkenyl-alkenyl cross-coupling reactions, the configurations of the vinylborane and vinyl halide coupling partners are retained.

The Suzuki coupling of compounds **100** and **101** (see Scheme 24) is especially interesting because it provides an efficient and elegant path for the synthesis of the indole nucleus. Exposure of the Suzuki coupling product **102** to the action of a mild acid induces



**Scheme 24.** Representative Suzuki couplings.



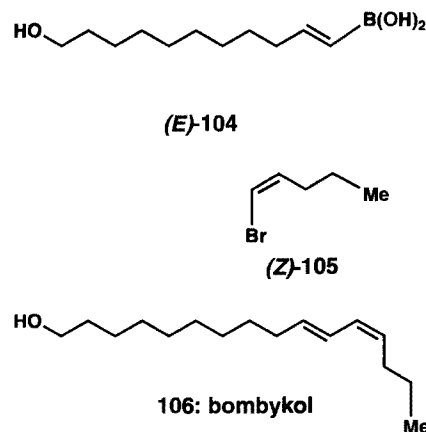
Scheme 25. Catalytic cycle for the Suzuki coupling.

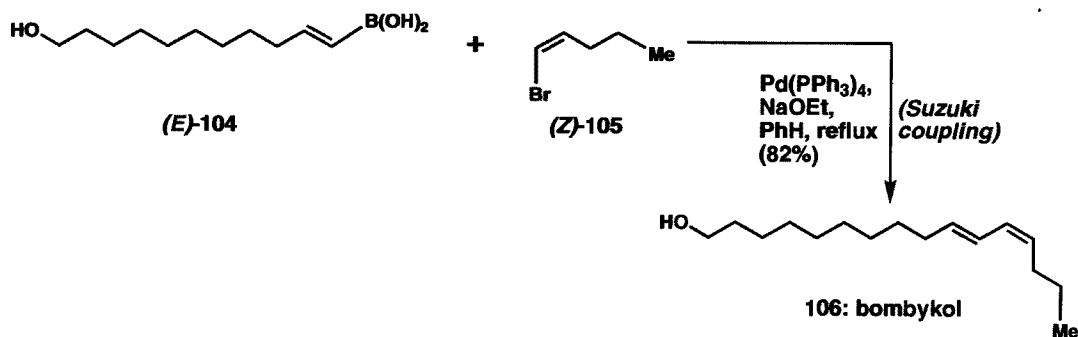
the formation of indole **103** in nearly quantitative yield. Similar chemistry could conceivably be used to prepare a wide variety of benzoheterocyclic compounds.

The postulated steps that constitute the Suzuki coupling process are shown in Scheme 25. After oxidative addition of the organic halide to the palladium(0) catalyst, it is presumed that a metathetical displacement of the halide substituent in the palladium(II) complex A by ethoxide ion (or hydroxide ion) takes place to give an alkoxopalladium(II) complex B. The latter complex then reacts with the alkenylborane, generating the diorganopalladium complex C. Finally, reductive elimination of C furnishes the cross-coupling product (D) and regenerates the palladium(0) catalyst.

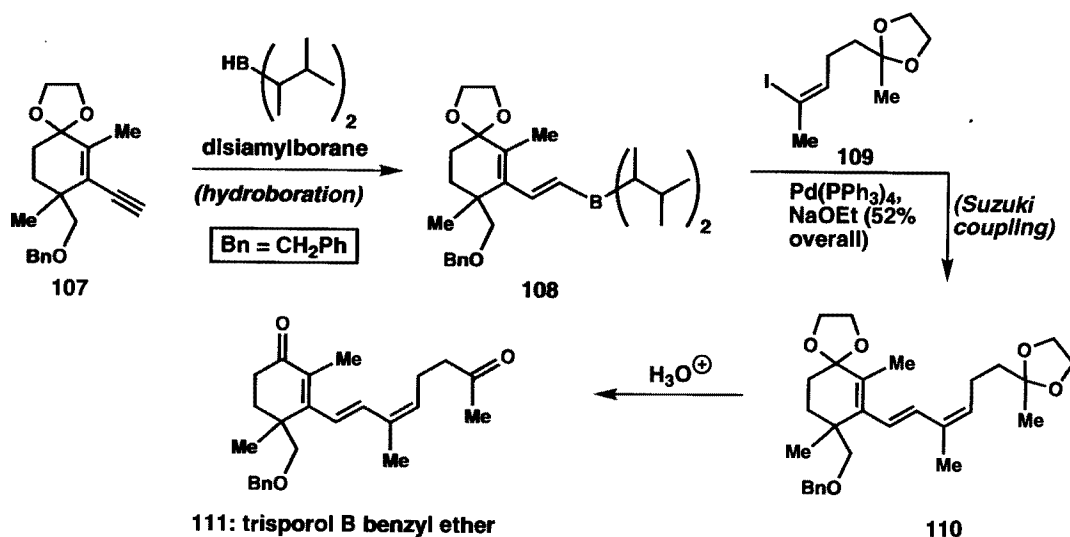
The utility of the Suzuki reaction in the challenging arena of natural product total synthesis has been explored. The constitution of bombykol (**106**) (see Scheme 26), a well-known pheromone, lends itself to a Suzuki coupling. Indeed, in a short stereospecific synthesis of **106**, Sugimoto et al. demonstrated that (*E*)-vinylboronic acid (*E*)-**104** can be smoothly cross-coupled with (*Z*)-1-pentenyl bromide [(*Z*)-**105**];⁴⁴ the configurations of both coupling partners are preserved in the C–C bond forming process.

A stereospecific Suzuki coupling is also the key step in the synthesis of trisporol B benzyl ether (**111**) by Suzuki et al. (see





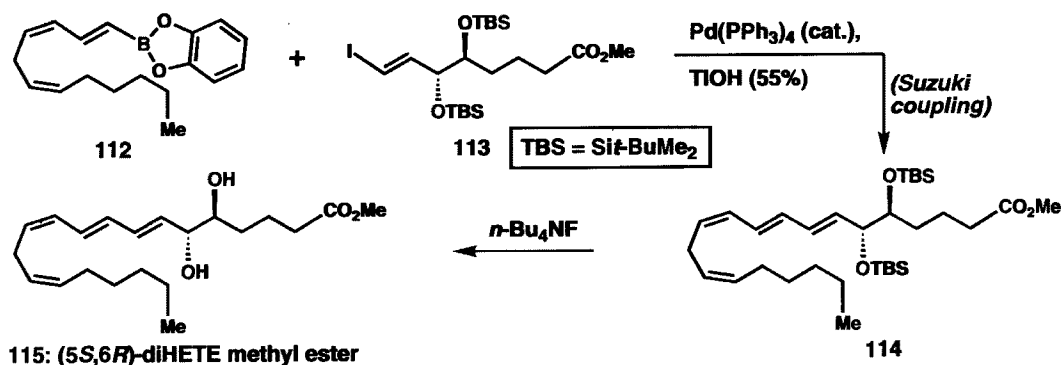
Scheme 26. The Suginome–Suzuki synthesis of bombykol (**106**).



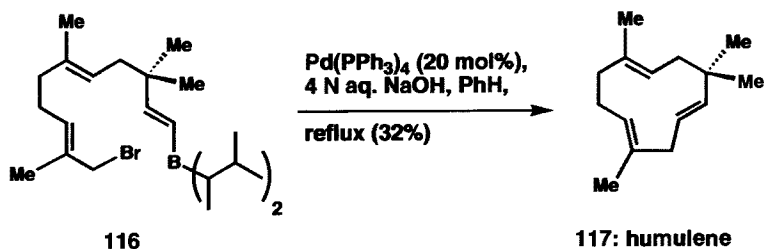
Scheme 27. Suzuki's synthesis of trisporol B benzyl ether (**111**).

Scheme 27).^{43b} A regioselective monohydroboration of enyne **107** with disiamylborane furnishes (*E*)-vinylborane **108**, a substance that combines stereospecifically with vinyl iodide **109** under the indicated conditions to give conjugated triene **110** (52% overall yield). Trisporol B benzyl ether (**111**) is obtained after acid-induced hydrolysis of the dioxolane ketal functions.

Using Kishi's modification of the Suzuki coupling procedure,⁴⁵ Nicolaou et al. accomplished the convergent union of compounds **112** and **113** (see Scheme 28).^{38b,46} This coupling is the key step in a synthesis of (5*S*,6*R*)-dihydroxyeicosatetraenoic acid [(5*S*,6*R*)-diHETE] methyl ester (**115**). Importantly, the configurations of the two coupling partners are reflected in the Suzuki coupling product **114**.



Scheme 28. Nicolaou's synthesis of (5S,6R)-diHETE methyl ester (**115**).



Scheme 29. The Suginome-Suzuki synthesis of humulene (**117**).

To illustrate the breadth of the Suzuki coupling process, it would be instructive to address the Suginome-Suzuki synthesis of humulene (**117**), a sesquiterpene found in the oil of hops (see Scheme 29).⁴⁷ Compound **117**, distinguished by a triply unsaturated eleven-membered cyclic framework, can be constructed by a palladium-catalyzed cyclization of compound **116**. In the event, a slow addition of **116** to a refluxing solution of benzene containing $\text{Pd(PPh}_3)_4$ (20 mol %) and 4 N aqueous NaOH brings about the desired intramolecular cross-coupling reaction and furnishes humulene **117** in 32 % yield.

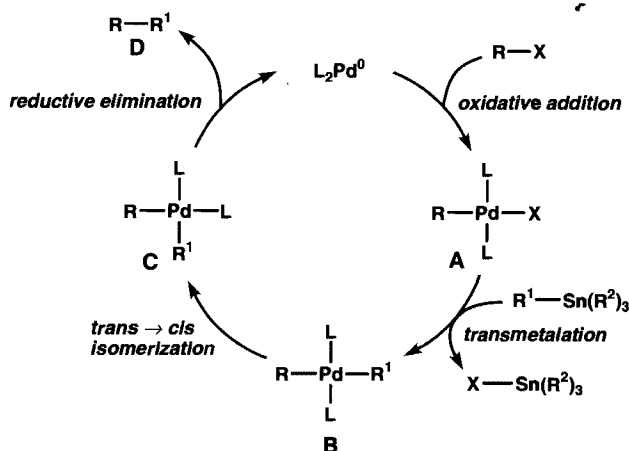
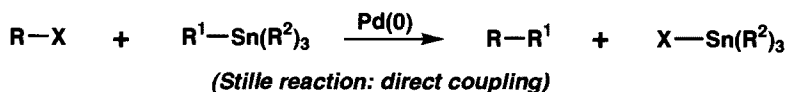
31.1.5 The Stille Coupling

The late Professor J. K. Stille pioneered the development of a very effective and versatile palladium-mediated C–C bond forming method – the palladium-catalyzed cross-coupling of organic electrophiles with organostannanes.⁴⁸ This process continues to enjoy much success in organic synthesis because it proceeds in high yields under mild reaction conditions and because it tolerates a

variety of functional groups (e.g. CO_2R , CN , OH , and even CHO) on either coupling partner. An additional virtue of this palladium-catalyzed coupling process is that a wide variety of organic electrophiles and organotin reagents can be utilized.

The Stille coupling process actually comprises two general reaction types. In one case, a direct union of an organic electrophile and an organotin reagent can be achieved through the agency of a palladium catalyst, usually tetrakis(triphenylphosphine)palladium(0) or benzylchlorobis(triphenylphosphine)palladium(II). In the other case, if the coupling reaction is simply conducted in the presence of carbon monoxide, the two coupling partners become linked through a carbonyl bridge, giving rise to a ketone. The catalytic cycles presented in Schemes 30 and 31 serve as working models for these two coupling variants.

In the direct coupling reaction (Scheme 30), it is presumed that a coordinatively unsaturated 14-electron palladium(0) complex such as bis(triphenylphosphine)palladium(0) serves as the catalytically active species. An oxidative addition of the organic electrophile, RX , to the palladium catalyst generates a 16-electron palladium(II) complex A, which then participates in a transmetalation with the organotin reagent (see $\text{A} \rightarrow \text{B}$). After facile *trans* \rightarrow *cis* isomerization (see $\text{B} \rightarrow \text{C}$), a reductive elimination releases the primary organic product D and regenerates the catalytically active palladium(0) complex.

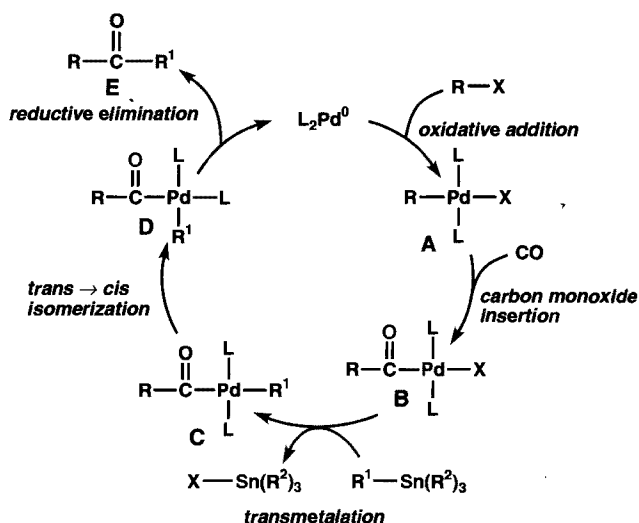
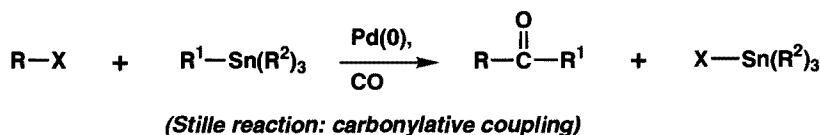


Scheme 30. Catalytic cycle for the Stille reaction: direct coupling.

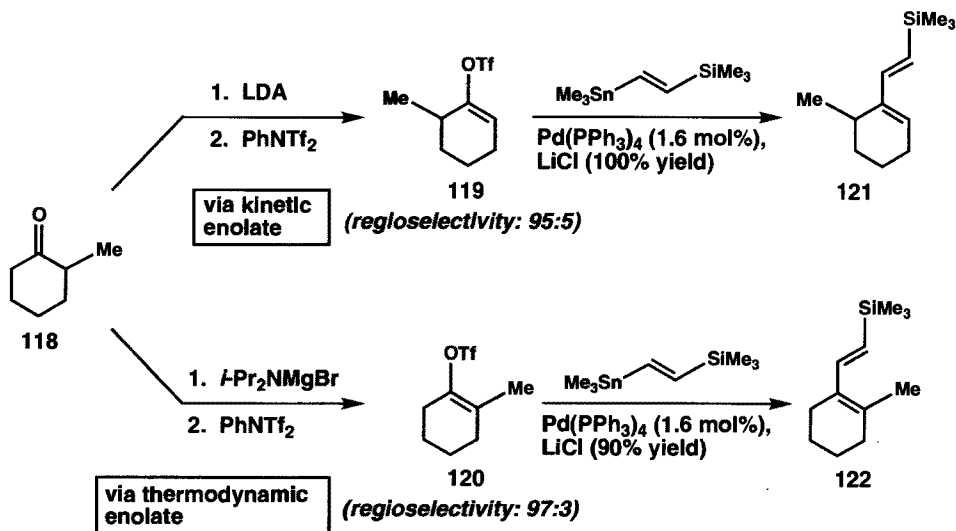
Although analogous to the direct coupling reaction, the catalytic cycle for the carbonylative coupling reaction is distinguished by an insertion of carbon monoxide into the C–Pd bond of complex A (see A → B, Scheme 31). The transmetalation step then gives *trans* complex C which isomerizes to the *cis* complex D. The ketone product E is revealed after reductive elimination.

The Stille coupling process can be regarded as the feature reaction of this chapter. In the first total synthesis of rapamycin (*vide infra*), the conjugated triene moiety and the 31-membered macrolide ring were fashioned in one operation by way of a tandem inter-/intramolecular Stille coupling strategy. Before we commence with a detailed discussion of this work, we will briefly address a few of the many exciting applications of the Stille coupling in synthesis.

The finding that vinyl triflates (also known as enol triflates) are effective electrophiles in palladium-catalyzed cross-couplings with organostannanes has significantly expanded the scope of the Stille reaction.⁴⁹ Vinyl triflates are conveniently formed by the trapping of enolate oxygens with reactive triflating agents such as *N*-phenyl-trifluoromethanesulfonimide (PhNTf₂).^{49c,50} The problem of gener-



Scheme 31. Catalytic cycle for the Stille reaction: carbonylative coupling.

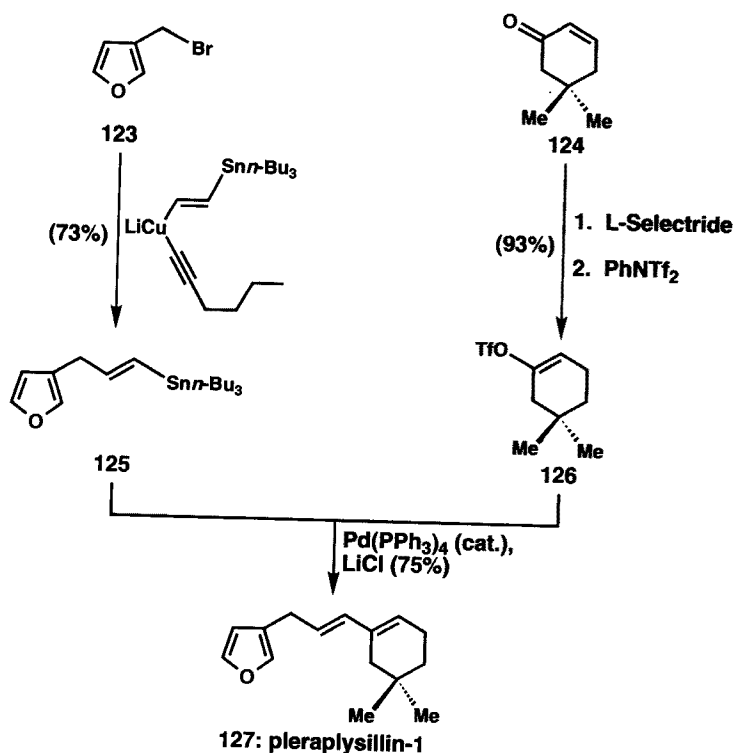


Scheme 32. Stille couplings of regioselectively generated enol triflates with a vinylstannane.

ating a vinyl triflate in a regio- and stereocontrolled fashion is thus one of defining the regio- and stereochemistry of the precursor enolate ion. In Stille applications, vinyl triflates offer a distinct advantage because effective methodology for the regio- and stereocontrolled enolization of carbonyl compounds is available.^{51,52} For example, 2-methylcyclohexanone (**118**) (see Scheme 32) can easily be converted to the corresponding kinetic (less substituted) lithium enolate by treatment with lithium diisopropylamide (LDA) and subsequently trapped with PhNTf₂ to give vinyl triflate **119** with 95:5 regioselectivity. On the other hand, the effective thermodynamic enolization procedure of Krafft and Holton⁵³ allows **118** to be converted, after enolate triflation, to vinyl triflate **120** with excellent (97:3) regioselectivity.

An important feature of the Stille reaction is that it is not particularly susceptible to steric effects. Indeed, vinyl triflate **120**, despite its somewhat hindered nature, couples smoothly with the indicated vinylstannane in the presence of a catalytic amount of Pd(PPh₃)₄ and LiCl to give 1,3-diene **122** in 90% yield (see Scheme 32).^{49a} As expected, vinyl triflate **119** is converted to the regioisomeric 1,3-diene **121** under identical conditions.

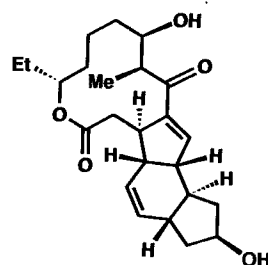
The key step in a short and efficient synthesis of pleraplysillin-1 (**127**) is the palladium-catalyzed cross-coupling of vinylstannane **125** with vinyl triflate **126** (see Scheme 33). This synthesis is noteworthy in two respects. First, vinyl triflate **126** is generated regio-specifically from the kinetic enolate arising from a conjugate reduction of enone **124**; the conjugate reduction of an enone is, in fact, a



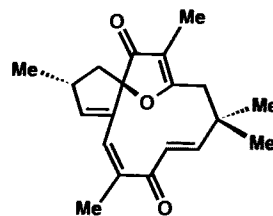
Scheme 33. Stille's synthesis of pleraplysillin-1 (**127**).

reliable method for the regiocontrolled formation of an enolate ion.^{51,54} Second, the *trans* stereochemistry of the vinylstannane coupling partner **125** is maintained in the Stille coupling.

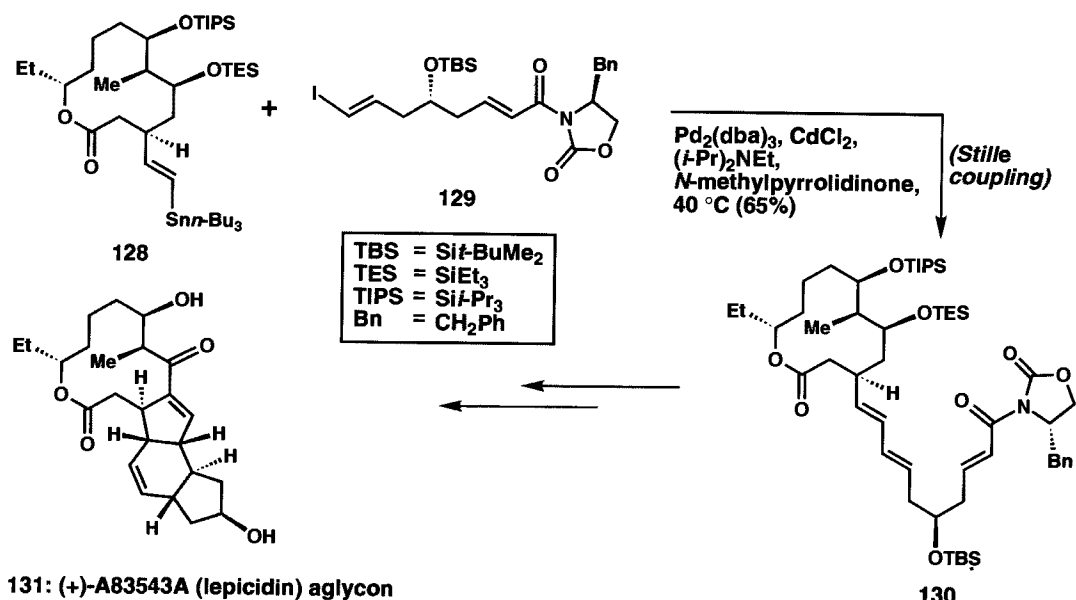
The facility with which organic electrophiles can be cross-coupled with organostannanes under the influence of a palladium(0) catalyst creates numerous productive possibilities in synthesis. For example, during the course of an asymmetric synthesis of the complex macrolide (+)-A83543A (lepicidin) aglycon (**131**), Evans and Black accomplished the convergent union of (*E*)-vinylstannane **128** and (*E*)-vinyl iodide **129** by a palladium(0)-catalyzed Stille reaction (see **128** + **129** → **130**, Scheme 34).⁵⁵ This union establishes a crucial C–C bond, and it should be noted that the configurations of both coupling partners are preserved in the cross-coupling reaction; the Stille coupling of **128** and **129** is thus stereospecific. The palladium-catalyzed intermolecular cross-coupling of vinyl triflate **132** with (*Z*)-vinylstannane **133** is also noteworthy (see Scheme 35). This nearly quantitative union constitutes a key step in Wiemer and Han's asymmetric total synthesis of (+)-jatrophone (**135**).⁵⁶



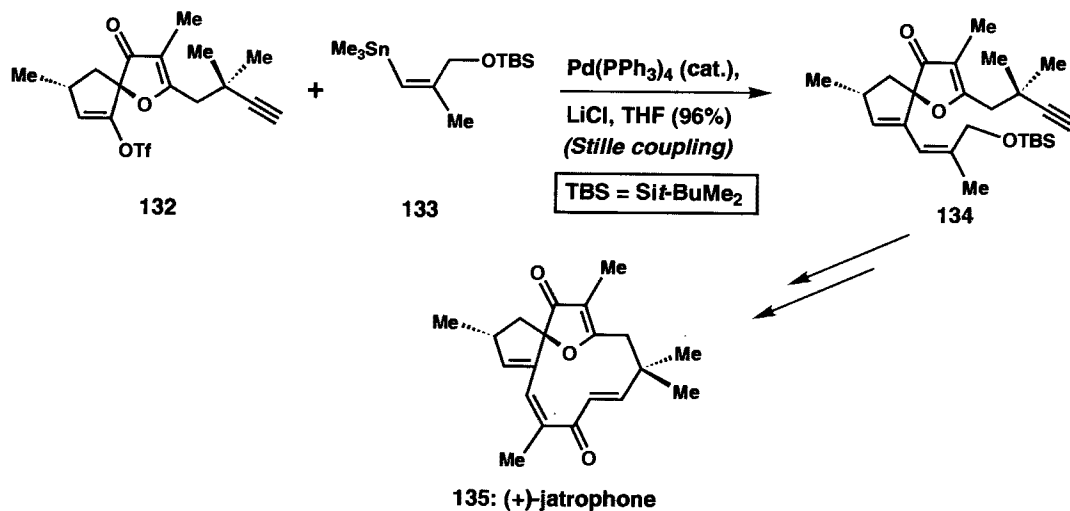
131: (+)-A83543A (lepicidin) aglycon



135: (+)-jatrophone

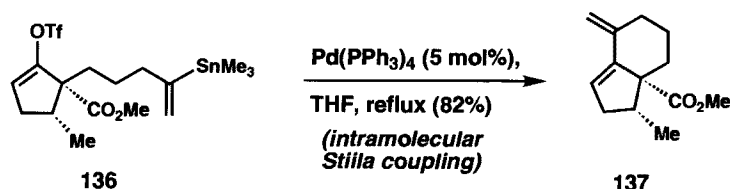


Scheme 34. The Stille reaction in Evans's synthesis of (+)-A83543A (lepidicin) aglycon (131).



Scheme 35. The Stille reaction in Wiemer and Han's synthesis of (+)-jatrophone (135).

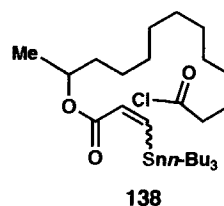
The Stille reaction is also effective as a ring-forming method. In an early contribution, Piers et al. demonstrated that novel bicyclic dienes such as **137** (see Scheme 36) can be efficiently constructed through a short reaction sequence in which an intramolecular Stille coupling constitutes the key step.⁵⁷ In the event, treatment of enol triflate vinylstannane **136** with a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ in refluxing THF induces an efficient ring closure, affording bicyclic diene **137** in 82% yield. This novel intramolecular coupling process was successfully applied to a number of enol triflate vinylstannanes, and would appear to be a general method for the annulation of five- and six-membered rings. Prior to this work, there were no recorded examples of intramolecular Stille couplings.

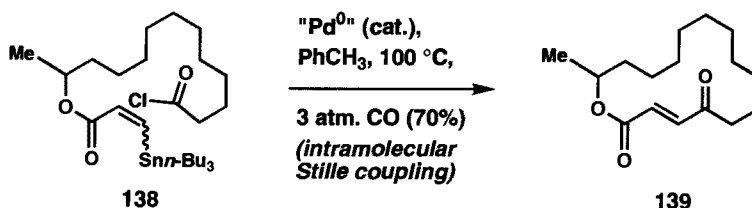


Scheme 36. Piers's annulation strategy based on the intramolecular Stille reaction.

As a cyclization method, the Stille reaction is not limited to the construction of five- and six-membered rings. Indeed, the intramolecular version of the Stille reaction is a versatile and most powerful method for the synthesis of medium-ring and macrocyclic structures. The impressive success of the Stille reaction in this regard is likely due, in large part, to the templating effect of the palladium metal center. In this reaction, the palladium catalyst serves as a template, bringing into proximity the two ends of a bifunctional chain. Expulsion of the palladium(0) catalyst in the terminating reductive elimination step is attended by the formation of a bond between the terminal carbon atoms, thus giving rise to a new cyclic molecule; strained medium rings can thus be formed through ring contraction of larger, less strained transitory palladacycles.

The palladium-catalyzed cyclization of compound **138** amply demonstrates the utility of the Stille reaction as a macrocyclization method (see Scheme 37). This efficient ring closure is just one of many examples disclosed by J.E. Baldwin and his group at Oxford.⁵⁸ Interestingly, compound **138** can be employed as a stereoisomeric mixture of vinylstannanes because both stereoisomers converge on the same cyclized product. To rationalize this result, it was suggested that the configuration of the vinylstannane moiety is conserved in the cyclization, but that the macrocycle resulting from the (*Z*)-vinylstannane stereoisomer isomerizes to the thermodynamically favored *trans* product under the reaction condi-





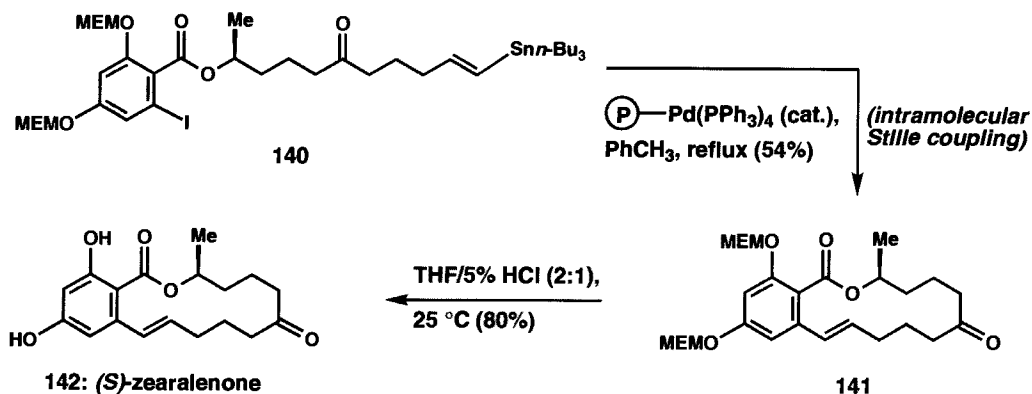
Scheme 37. Baldwin's approach to γ -oxo- α,β -unsaturated macrocycles by intramolecular Stille coupling.

tions. This methodology was used to prepare a series of γ -oxo- α,β -unsaturated macrolides ranging in size from 10–20 members with good efficiency. Incidentally, although Stille couplings of acid chlorides with vinylstannanes can be accomplished in the absence of carbon monoxide, the cyclization of **138** to give **139** was found to be more efficient in an atmosphere of carbon monoxide; the presence of CO may suppress the decarbonylation of the acid chloride in the Stille cyclization event.

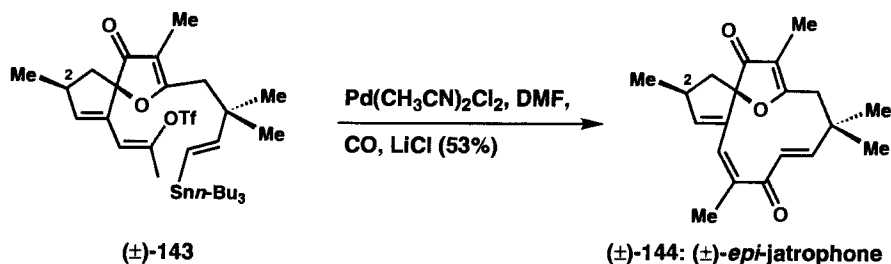
An intramolecular palladium(0)-catalyzed cross-coupling of an aryl iodide with a *trans* vinylstannane is the penultimate maneuver in the Stille–Hegedus total synthesis of (*S*)-zearalenone (**142**) (see Scheme 38).⁵⁹ In the event, exposure of compound **140** to Pd(PPh₃)₄ catalyst on a 20% cross-linked polystyrene support in refluxing toluene brings about the desired macrocyclization, affording the 14-membered macrolide **141** in 54% yield. Acid-induced hydrolysis of the two methoxyethoxymethyl (MEM) ethers completes the total synthesis of **142**.

It is fitting to conclude this short treatise on the use of the Stille reaction in organic synthesis with an elegant contribution from the groups of Stille and Hegedus.⁶⁰ The palladium-catalyzed cyclization of compound (\pm)-**143** (see Scheme 39) with interpolation of a molecule of carbon monoxide can accomplish the construction of *epi*-jatrophone's macrocyclic ring. Under the indicated conditions, vinyl triflate vinylstannane (\pm)-**143** is transformed to (\pm)-*epi*-jatrophone [(\pm)-**144**] in 53% yield. (\pm)-Jatrophone [(\pm)-**135**] can be prepared from the C-2 epimer of (\pm)-**143** by the same palladium-catalyzed carbonylative cross-coupling reaction, although in lower yield.

Our general survey of palladium in organic synthesis must now come to an end. At the very least, we hope that our brief foray into this fascinating area conveys some of the vitality that characterizes research in this area. The remainder of this chapter will address the first total synthesis of rapamycin by the Nicolaou group. This work is predicated on a novel variant of the Stille reaction.



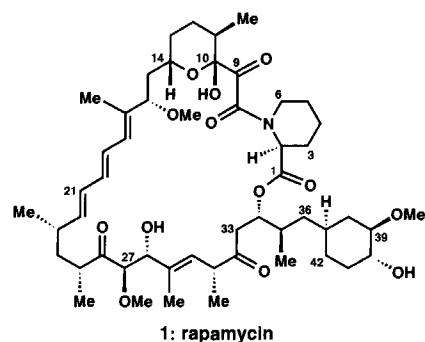
Scheme 38. The Stille–Hegedus synthesis of (S)-zearalenone (142).



Scheme 39. The Stille–Hegedus synthesis of (±)-epi-jatrophone [(±)-144].

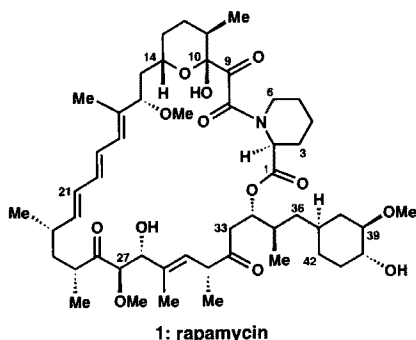
31.2 Retrosynthetic Analysis and Strategy

Rapamycin (**1**), is a striking molecular assembly comprising fifty-one carbons, seventy-eight hydrogens, thirteen oxygens, and one nitrogen. Its 31-membered macrocyclic structure conceals a vicinal tricarbonyl moiety, and is further distinguished by fifteen stereogenic centers, numerous electrophilic functional groups, and a conspicuous all-*trans* conjugated triene. It is interesting to note that the C-10 carbonyl is engaged as an internal hemiketal with the hydroxyl group attached to C-14. Although the macrolide has the potential for ring-chain tautomerism, rapamycin exhibits a large equilibrium preference for the closed hemiketal form in both solution and solid states. There is, however, an equilibrium in solution between



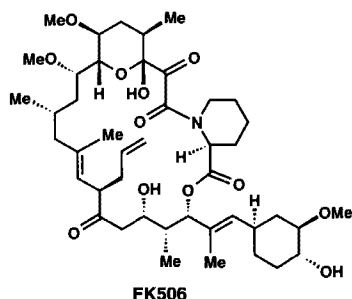
the pyrano hemiketal shown in **1** and an isomeric seven-membered hemiketal involving the C-9 carbonyl and the C-14 hydroxyl group.⁶¹ The natural product is also susceptible to an equilibrium between two amide bond rotamers.

The X-ray crystal structure of rapamycin reveals the constitution of the major isomer, compound **1**, although in solution at least four isomers are detectable. The most abundant isomers are **1** (major) and the isomeric seven-membered hemiketal (mixture of stereoisomers). For the purposes of this chapter, we will restrict ourselves to structure **1**.



The rapamycin molecule, with its numerous electrophilic and potentially labile functional groups, is prone to several destructive pathways in a basic medium. Indeed, kinetic enolization of the C-32 ketone with concomitant β -elimination of the C-34 lactone oxygen, C9–C10 benzylic acid rearrangement,⁶⁴ and retroaldol cleavage of the C27–C28 bond can all take place when **1** is exposed to basic reagents. Of these three destructive processes, the first is particularly facile; the action of even mildly basic reagents such as Et₃N or NaHCO₃ in methanol on **1** causes rupture of the macrocycle through β -elimination of the C-34 lactone oxygen. Interestingly, in the X-ray crystal structure of rapamycin, the C-34 lactone oxygen is roughly perpendicular to the C-32 carbonyl π -system, a circumstance that would favor β -elimination.

A conspicuous structural feature of rapamycin is the β -hydroxy ketone moiety at positions 26–28. β -Hydroxy ketones are familiar groupings that can participate in destructive retroaldol cleavage and/or dehydration reactions in the presence of strong base.^{54a} Rapamycin's β -hydroxy ketone moiety is no exception, for it suffers ready retroaldol cleavage upon exposure to competent bases.^{62,63} Interestingly, a retroaldol cleavage of the C27–C28 bond in **1** can also be effected by the Lewis acid ZnCl₂.^{62a} In THF, the action of ZnCl₂ on rapamycin causes a selective retroaldol cleavage of the C27–C28 bond, whereas ZnCl₂ in MeOH accomplishes both C27–C28 retroaldol cleavage and a C9–C10 benzylic acid rearrangement.⁶⁴ In light of all these observations, it would be prudent for any total synthesis plan to avoid exposing the natural product to strongly basic or Lewis acidic species.

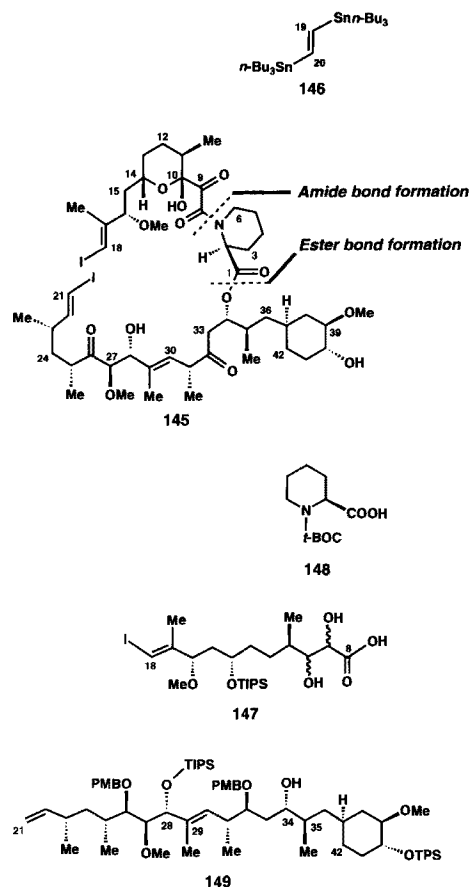


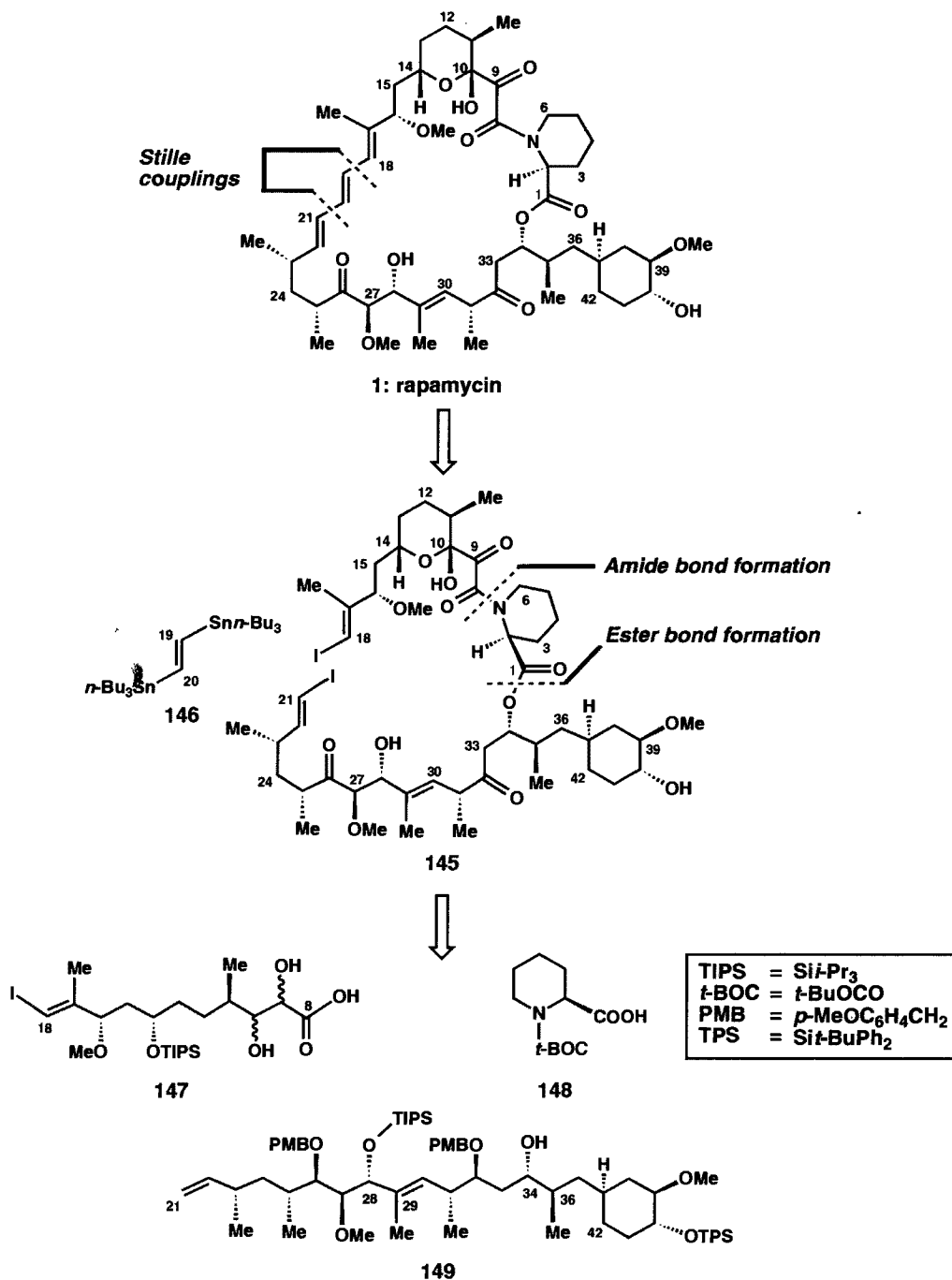
In considering a retrosynthetic analysis of rapamycin (**1**), it is instructive to recall two independent total syntheses of the related natural product FK506 by two groups: one from Merck⁶⁵ and one from Harvard.⁶⁶ In both cases, the macrocyclic ring (a 21-membered system containing a very similar C1–C14 segment) was constructed from an open-chain precursor by lactamization, an option also available for rapamycin's construction (N7–C8 bond formation). But in addition to this productive possibility, the O–C1 and C27–C28 bonds in rapamycin are also attractive as sites for retrosynthetic disassembly. In the synthetic direction, a macro-lactonization reaction to form the O–C1 ester bond or an intramolecular aldol reaction to form the C27–C28 bond could, in theory, be applied to the task of constructing rapamycin's 31-mem-

bered ring. Conformational rigidity conferred to the backbone of the seco substrate (the open-chain precursor) by the conjugated triene moiety would likely benefit all three of these macrocyclization options.

At this preliminary stage of our analysis, we were thus mindful of three different macroring forming strategies, one of which, the macrolactamization option, appeared to rest on strong precedent. Nevertheless, in a deliberate effort to advance a new concept for the construction of polyene macrolides, yet another possibility was considered. One of rapamycin's most salient structural features is the all-*trans* conjugated triene segment encompassing carbons 17–22. Prior experiences in our laboratory provided a basis for concerns regarding the stability of conjugated polyenic arrays, and we, therefore, decided that it would be wise to defer the installation of the rapamycin triene to a late stage in the synthesis. In an ideal situation, it would be possible to construct the conjugated triene and the macrocycle in the same step under mild reaction conditions. Although an intramolecular Wittig-type reaction seemed well suited to this goal, the notion of inserting a C19–C20 ethylene unit between carbons 18 and 21 by a tandem inter-/intramolecular Stille coupling strategy was particularly attractive (see Scheme 40); the Stille reaction is an effective C–C bond forming method that proceeds under mild reaction conditions. Thus, retrosynthetic disassembly of the rapamycin molecule in the manner illustrated in Scheme 40 furnishes *trans*-1,2-bis-(tri-*n*-butylstannyl)ethylene (**146**) and bis(vinyl iodide) **145** as potential precursors. It was anticipated that under the influence of a palladium catalyst, the two-carbon linker **146** would participate in an intermolecular Stille coupling with the less hindered vinyl iodide grouping in **145** (i.e. at C-21). The resulting C-18 vinyl iodide/C-19 vinylstannane would then be poised for an intramolecular Stille coupling to give rapamycin. This “stitching cyclization” strategy would thus be applied to a fully deprotected seco substrate **145**, and, if successful, would represent a new approach to the construction of polyene macrolides.

Of all the bonds contained within intermediate **145**, the O–C1 ester and N–C8 amide bonds are among the most logical sites for retrosynthetic disassembly. Retrosynthetic simplification of **145** by cleavage of these two bonds furnishes, after some functional group and oxidation state adjustments, fragments **147**, **148**, and **149**. In the forward sense, it seemed reasonable to expect that activation of the carboxyl function of *N*-*t*-BOC-L-pipecolic acid **148**, in the presence of intermediate **149**, would permit the construction of the O–C1 ester bond. The amide bond could then be formed after removal of the *tert*-butylcarbamate (*t*-BOC) protecting group, followed by acylation of the liberated nitrogen with an activated ester derived from **147**. While intermediate **148** is easily derived from commercially available L-pipecolic acid, intermediates **147** and **149** are rather complex and would have to be synthesized from simpler building blocks.





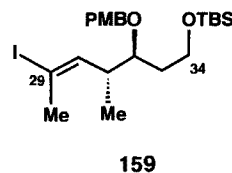
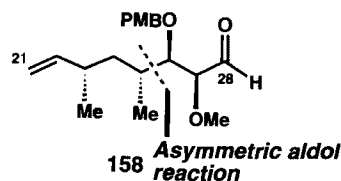
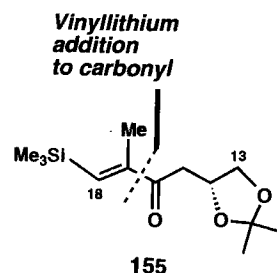
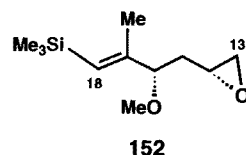
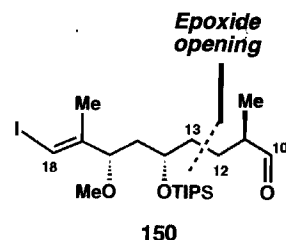
Scheme 40. Retrosynthetic analysis of rapamycin (1).

It is worth pointing out that the stereochemistry of intermediate **147** at C-9 and C-10 is inconsequential since both positions will eventually bear trigonal carbonyl groups in the final product. The synthetic problem is thus significantly simplified by virtue of the fact that any or all C9–C10 diol stereoisomers could be utilized. A particularly attractive means for the construction of the C9–C10 bond and the requisite C8–C10 functionality in **147** is revealed by the disconnection shown in Scheme 41. It was anticipated that the venerable intermolecular aldol reaction could be relied upon to accomplish the union of aldehyde **150** and methyl glycolate (**151**) through a bond between carbons 9 and 10.

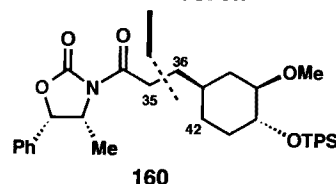
Aldehyde **150**, distinguished by a *trans* vinyl iodide moiety and three stereogenic centers, can be traced retrosynthetically to compounds **152** and **153** by disassembly of the C12–C13 bond and functional group manipulations. There is good reason to believe that iodide **153** could be converted to an organometallic species and that the latter would then attack the less hindered terminal carbon of epoxide **152** to give the requisite C12–C13 bond. A noteworthy feature of our approach to the synthesis of the C8–C18 fragment **147** is the use of a vinyl silane as a surrogate for a vinyl iodide; vinyl silanes can be transformed to vinyl iodides with retention of geometry through reaction with various sources of electrophilic iodine.⁶⁷

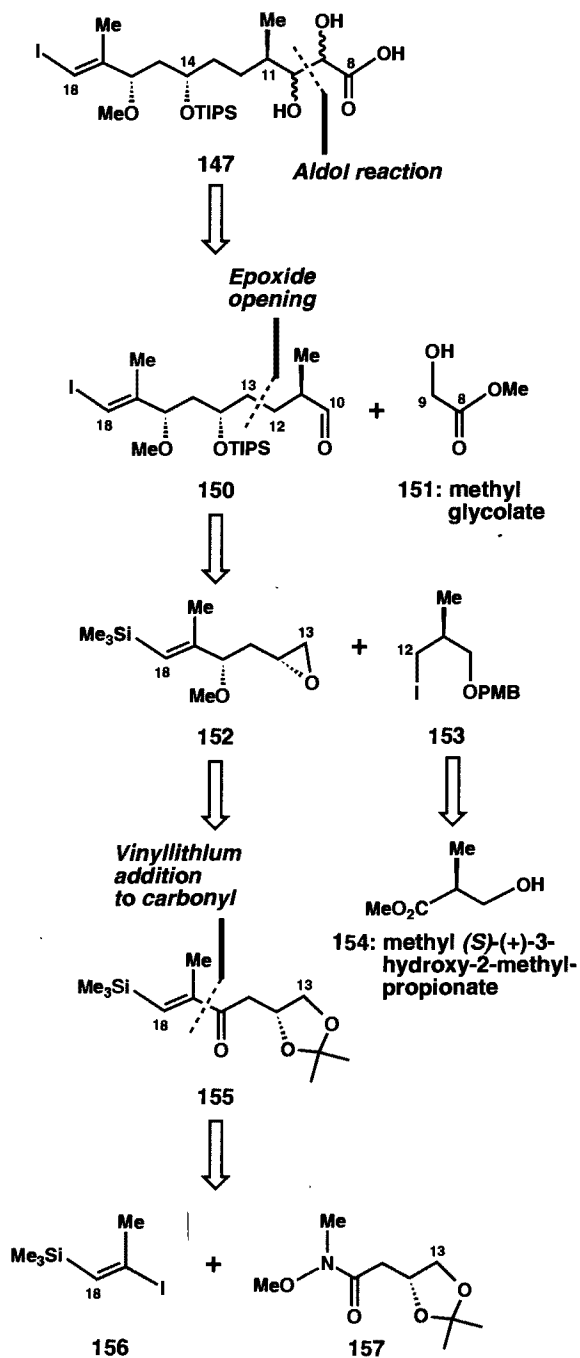
A retrosynthetic analysis of fragment **152** can be completed through cleavage of the C16–C17 bond in enone **155**, the projected precursor of epoxide **152**. This retrosynthetic maneuver furnishes intermediates **156** and **157** as potential building blocks. In the forward sense, acylation of a vinyl metal species derived from **156** with Weinreb amide **157** could accomplish the construction of enone **155**. Iodide **153**, on the other hand, can be traced retrosynthetically to the commercially available, optically active building block methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**154**).

Compound **149**, the host of twelve stereogenic centers, a trisubstituted cyclohexane ring, a *trans* trisubstituted double bond, and numerous differentiated oxygen atoms, is very complex. Its constitution is, however, amenable to two very productive retrosynthetic maneuvers (Scheme 42). Disassembly of the indicated C–C bonds in **149** provides three fragments, **158**, **159**, and **160**, of roughly equal complexity. Collectively, these three building blocks account for nine of the twelve stereogenic centers found in **149**; it was our hope that the remaining three could be introduced during the course of stereocontrolled coupling reactions. In particular, the oxygen-bearing C-28 stereocenter and the C28–C29 bond in **149** could conceivably be fashioned simultaneously by a Ni^{II}/Cr^{II}-mediated Nozaki–Takai–Hiyama–Kishi coupling⁶⁸ of compounds **158** and **159**. The required stereochemistry at C-28 would prevail if the carbonyl addition exhibits either Cram–Felkin–Anh or β -chelation-controlled diastereoselectivity. The C34–C35 bond, on the other hand, was projected to arise from an Evans asymmetric aldol condensation⁶⁹ between a C-34 aldehyde and a boron enolate derived

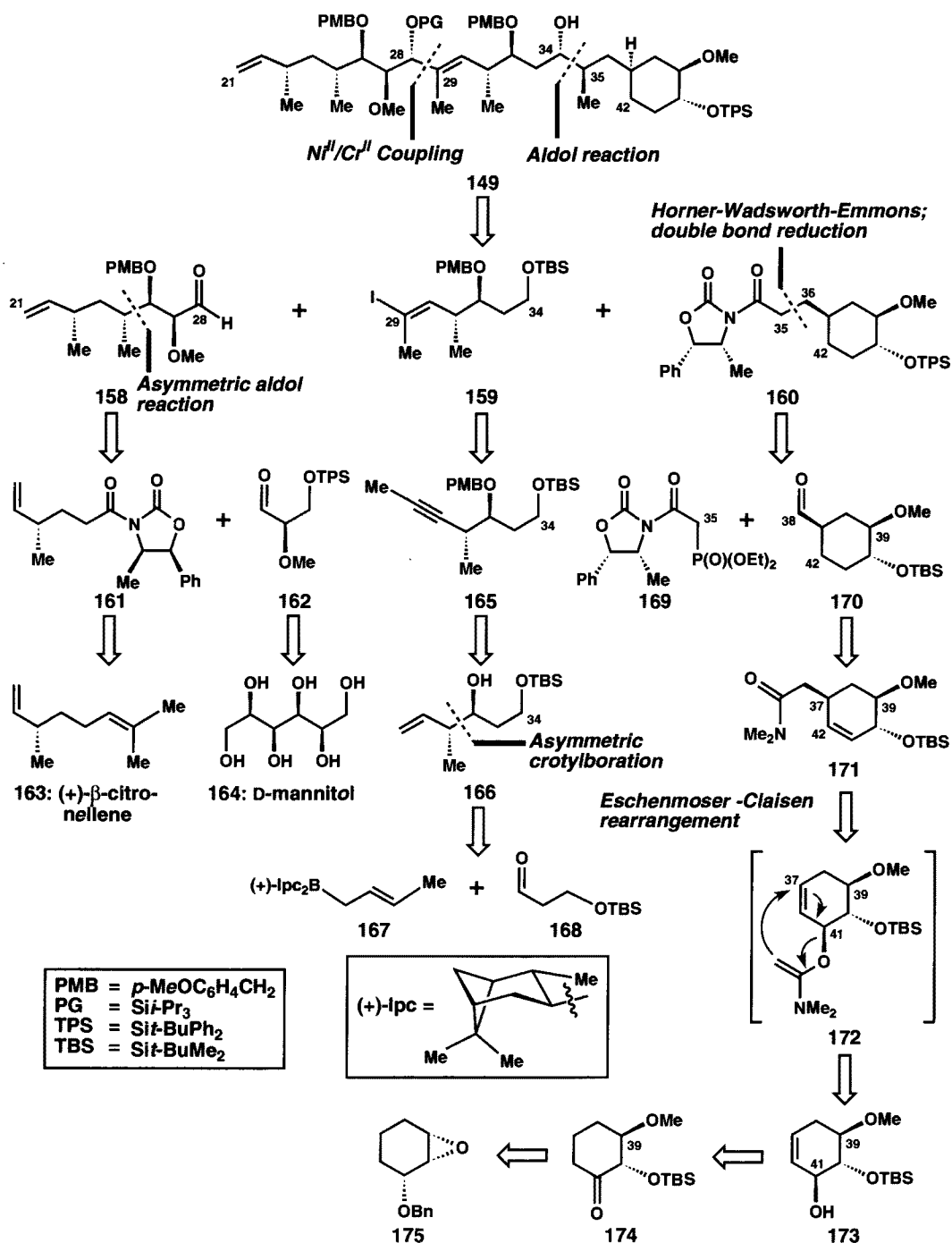


**Horner-Wadsworth-Emmons;
double bond reduction**



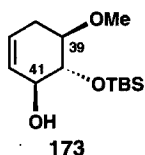
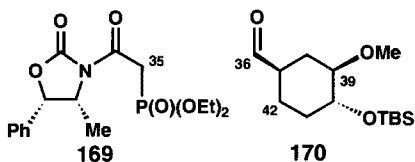
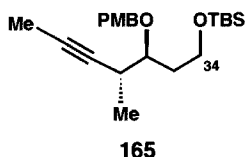
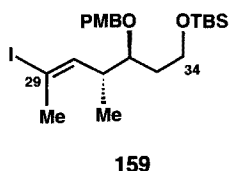
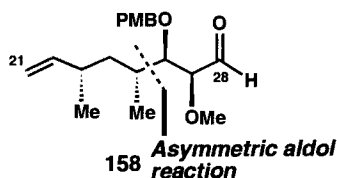
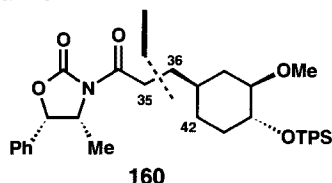


Scheme 41. Retrosynthetic analysis of the C8-C18 fragment **147**.



Scheme 42. Retrosynthetic analysis of the C21–C42 fragment 149.

**Horner-Wadsworth-Emmons;
double bond reduction**



from oxazolidinone **160** (see **209+160**→**210**, Scheme 51). On the basis of substantial precedent, there was good reason to believe that such a coupling would exhibit excellent *syn* diastereoselectivity and that the norephedrine-derived chiral auxiliary would define the absolute stereochemistry at carbons 34 and 35. After it has served its purpose as a stereocontrolling device, the chiral auxiliary in aldol adduct **210** (Scheme 51) would have to be reductively cleaved. Further reduction of the resulting hydroxy methyl group could furnish the requisite C-35 methyl group.

A similar Evans asymmetric aldol/reduction sequence could also serve well in a synthesis of fragment **158**. Compounds **161** and **162** thus emerge as potential precursors to **158**. In theory, building blocks **161** and **162** could be procured in optically active form from commercially available and enantiomerically pure (+)- β -citronellene (**163**) and D-mannitol (**164**), respectively (see Scheme 42).

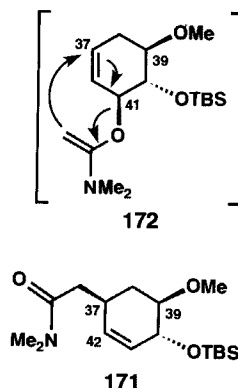
A valuable feature of the $\text{Ni}^{\text{II}}/\text{Cr}^{\text{II}}$ -mediated Nozaki-Takai-Hiyama-Kishi coupling of vinyl iodides and aldehydes is that the stereochemistry of the vinyl iodide partner is reflected in the allylic alcohol coupling product, at least when disubstituted or *trans* trisubstituted vinyl iodides are employed.⁶⁸ It is, therefore, imperative that the *trans* vinyl iodide stereochemistry in **159** be rigorously defined. Of the various ways in which this objective could be achieved, a regioselective *syn* addition of the Zr-H bond of Schwartz's reagent (Cp_2ZrHCl) to the alkyne function in **165**, followed by exposure of the resulting vinylzirconium species to iodine, seemed to constitute a distinctly direct solution to this important problem. Alkyne **165** could conceivably be derived in short order from compound **166**, the projected product of an asymmetric crotylboration of achiral aldehyde **168**.

Carboximide **160**, the C35-C42 fragment, can be traced retrosynthetically to phosphonate **169** and aldehyde **170**. In the synthetic direction, the C35-C36 bond in **160** could be constructed by an intermolecular Horner-Wadsworth-Emmons (HWE)⁷⁰ coupling of intermediates **169** and **170**. Reduction of the unsaturated coupling product and exchange of silyl protecting groups would then furnish compound **160**.

With three stereogenic centers and two differentiated oxygens, compound **170** poses a worthy synthetic challenge. Aldehyde **170** is the cyclohexane sector and it comprises carbons 36-42 of the natural product. In principle, **170** could be derived from unsaturated amide **171**. This retrosynthetic maneuver may seem strange in that it introduces functionality and would appear to complicate the synthetic problem. Nevertheless, compound **171** possesses a functional group relationship that satisfies the structural prerequisite for a reliable transformation in organic synthesis. Indeed, the conspicuous γ,δ -unsaturated amide in **171** constitutes the retron for the powerful Eschenmoser-Claisen rearrangement transform.⁷¹ Amide **171** can thus be traced retrosynthetically to allylic alcohol **173**. In the synthetic direction, subjection of **173** to the conditions of an Eschenmoser-Claisen rearrangement⁷² could furnish, via the ketene

N,O-acetal intermediate **172**, γ,δ -unsaturated amide **171**. It is important to note that there is a correspondence between the stereochemistry at C-41 of the allylic alcohol substrate **173** and at C-37 of the amide product **171**. Provided that the configuration of the hydroxyl-bearing carbon in **173** can be established as shown, then the subsequent suprafacial [3,3] sigmatropic rearrangement would ensure the stereospecific introduction of the C-37 side chain; during the course of the Eschenmoser–Claisen rearrangement, stereochemistry is transferred from C-41 to C-37. Ketone **174**, a potential intermediate for a synthesis of **173**, could conceivably be fashioned in short order from epoxide **175**.

The retrosynthetic analysis described above provides a highly convergent strategy towards rapamycin (**1**). While the coupling processes chosen to assemble the molecule are powerful enough to inspire a high degree of confidence, a number of stereochemical issues remain to be determined experimentally. The successful execution of this general strategy is discussed below.

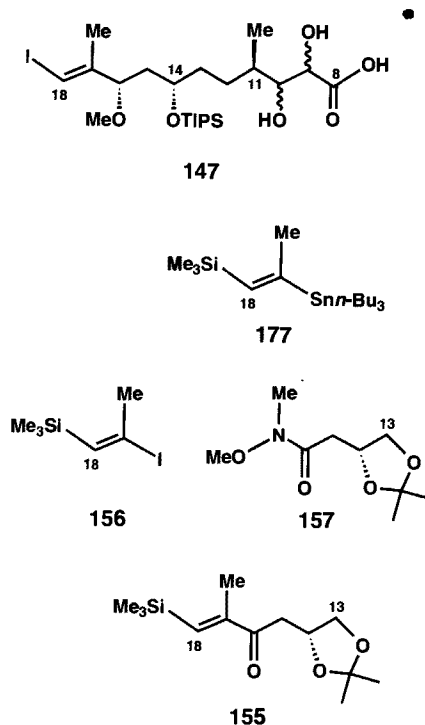


31.3 Total Synthesis

31.3.1 Synthesis of Intermediates **147** and **158–160**

The construction of dihydroxy acid **147**, the C8–C18 fragment, commences with a regioselective molybdenum-catalyzed *cis*-hydrostannylation of commercially available 1-trimethylsilylpropyne (**176**), affording compound **177** (Scheme 43). Although either the vinylsilyl or the vinylstannyl grouping in **177** could, in principle, be replaced with a suitable electrophile, compound **177** reacts smoothly and chemoselectively with iodine to give the versatile two-carbon synthon **156** (81% yield from **176**). In a parallel experiment, carboxylic acid **178**, a readily available derivative of L-ascorbic acid, can be easily converted to Weinreb amide **157**⁷³ by treatment with 1,3-dicyclohexylcarbodiimide (DCC) and $\text{NHMe(OMe)}\cdot\text{HCl}$ (70% yield). It was our hope that vinyl iodide **156** could serve as a precursor to a nucleophilic vinyl lithium reagent and that the latter species would attack the electrophilic carbonyl carbon of Weinreb amide **157**. In the event, subjection of **156** to the action of *tert*-butyllithium (≥ 2 equiv.) brings about an iodine–lithium exchange reaction, generating the putative organometallic species. Now, when a cold (-78°C) solution of the newly formed vinyl lithium reagent is exposed to Weinreb amide **157**, the desired *C*-acylation reaction takes place and enone **155** is produced in 70% yield.

With an oxygen-bearing stereocenter in proximity to the C-16 ketone carbonyl in **155**, the prospects for achieving a diastereoselective ketone reduction seemed favorable. From the work of Mori and Suzuki, it was known that similarly constituted ketones are amenable to β -chelation-controlled reductions with lithium alumi-



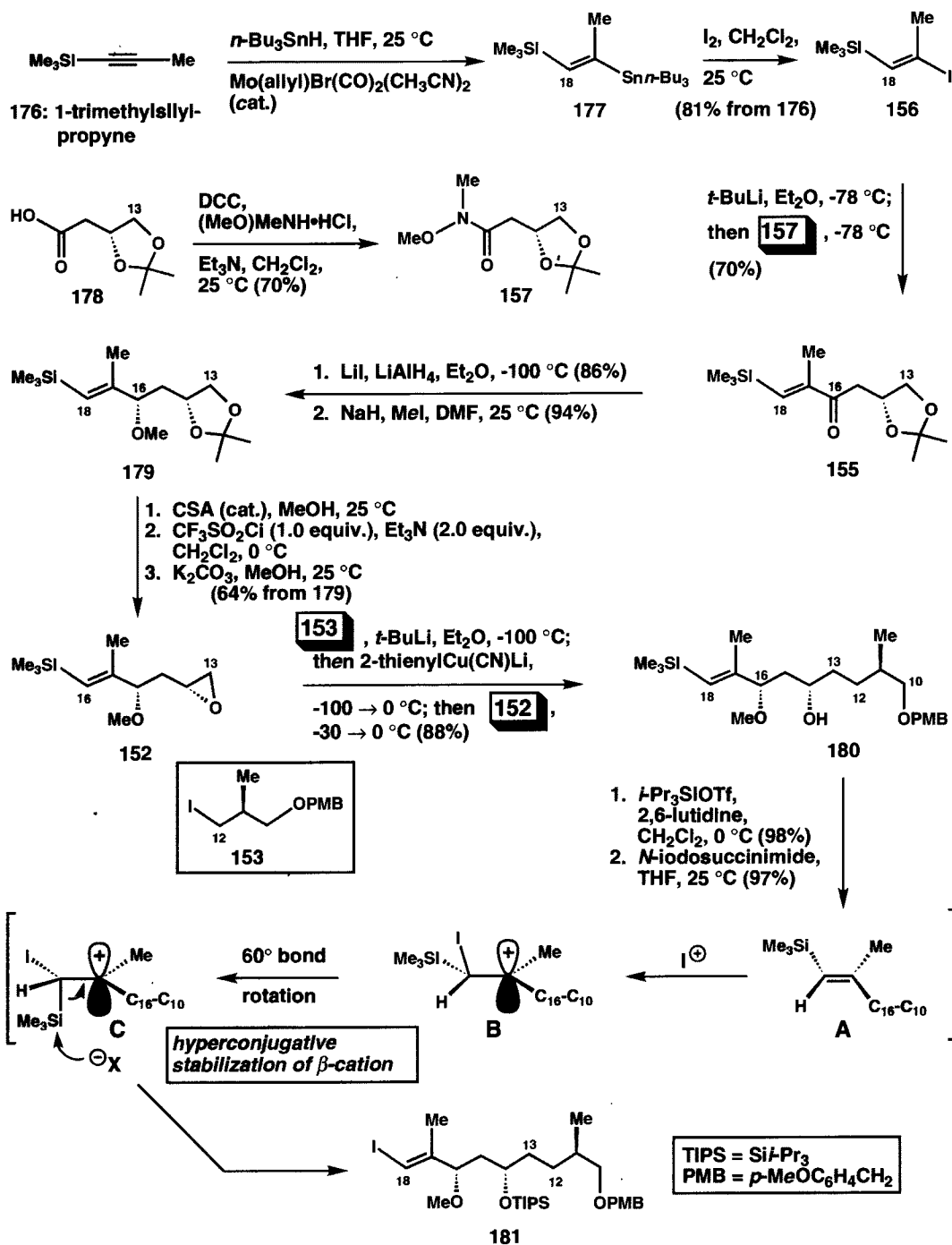
num hydride, provided that a suitable Lewis acid such as lithium iodide is also present.⁷⁴ Gratifyingly, treatment of enone **155** with lithium iodide and lithium aluminum hydride in ether at -100°C furnishes a single allylic alcohol diastereoisomer, the desired stereoisomer, in 86% yield. Alkylation of the newly formed secondary hydroxyl with sodium hydride and methyl iodide then provides methyl ether **179** in 94% yield. The observed stereochemical course of the 1,2-reduction of **155** is consistent with β -chelation control.

Having established the requisite oxygen-bearing stereocenter at position 16, we then found ourselves faced with the task of converting the isopropylidene ketal (acetonide) in **179** to an oxirane ring. For this purpose, the standard three-step sequence shown in Scheme 43 was found to be convenient. As expected, addition of a catalytic amount of camphorsulfonic acid (CSA) to a solution of **179** in methanol at 25°C causes solvolytic cleavage of the acetonide protecting group, providing the corresponding diol in good yield. In the presence of a stoichiometric amount of trifluoromethanesulfonyl chloride and triethylamine, the less hindered primary hydroxyl is converted smoothly and selectively to the corresponding triflate. The latter substance, a hydroxy sulfonate ester, participates in an intramolecular etherification reaction upon treatment with potassium carbonate to give epoxide **152**. The electrophilic character of the newly formed oxirane ring will play a key role in the elaboration of the C8–C18 intermediate **147**.

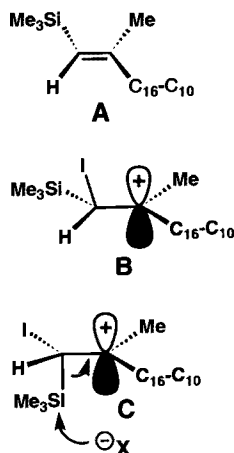
The optically active iodide **153** (Scheme 43) can be conveniently prepared from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**154**) (see Scheme 41). At this stage of the synthesis, our plan called for the conversion of **153** to a nucleophilic organometallic species, with the hope that the latter would combine with epoxide **152**. As matters transpired, we found that the mixed higher order cuprate reagent derived from **153** reacts in the desired and expected way with epoxide **152**, affording alcohol **180** in 88% yield; this regioselective union creates the C12–C13 bond of rapamycin.

It was anticipated all along that the vinylsilane residue could serve as a vinyl iodide surrogate. After protection of the C-14 secondary hydroxyl in **180** in the form of a triisopropylsilyl ether, the vinyltrimethylsilyl function can indeed be converted to the requisite vinyl iodide with *N*-iodosuccinimide (NIS) (see **180** \rightarrow **181**, Scheme 43). Vinyl iodide **181** is produced stereospecifically with retention of the $\Delta^{17,18}$ double bond geometry. This transformation is stereospecific since the stereochemistry of the starting vinylsilane and the vinyl iodide product bear a definite relationship to each other.^{67b,75}

A short digression is in order at this juncture. The electrophilic substitution of a vinylsilane is a very useful process because it is generally both regio- and stereospecific. The carbon–silicon bond is strongly polarized due to the high electronegativity of carbon (2.35) relative to silicon (1.64).^{67b} A unique and important conse-

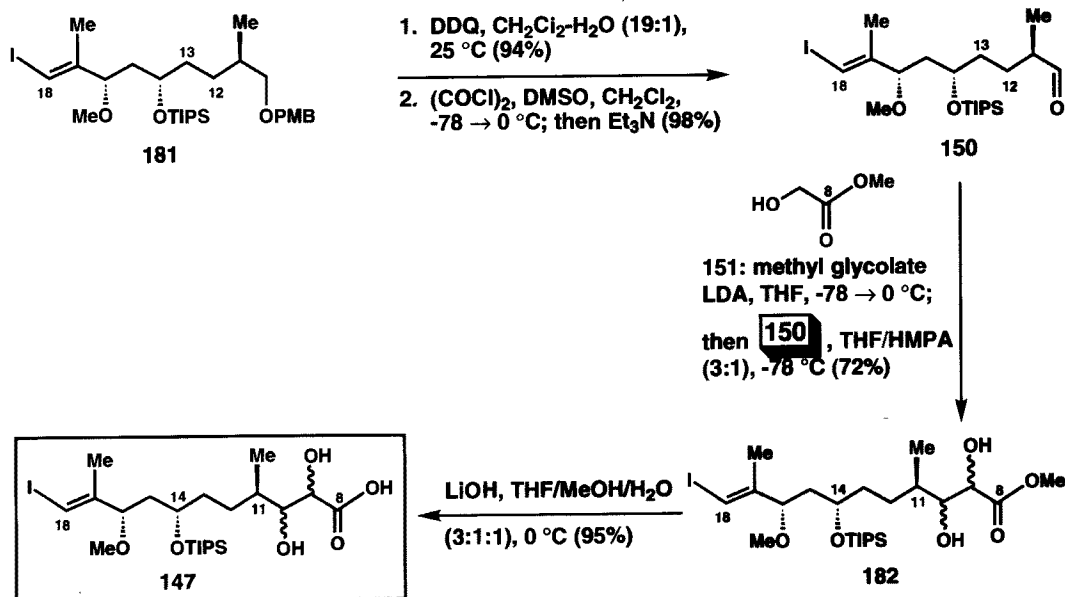


Scheme 43. Synthesis of intermediate 181.



quence of this bond polarization is that a positive charge β to silicon is stabilized by overlap of the carbon-silicon σ bond with the vacant p orbital of the adjacent carbocation; this hyperconjugative stabilization of a β -cation by a carbon-silicon σ bond is known in the literature as the β -effect. When a configurationally defined vinylsilane such as A (Scheme 43) is treated with a suitable electrophile (e.g. *N*-iodosuccinimide), a regioselective bond formation occurs between the electrophile, I^+ , and the silicon-bearing carbon (see A \rightarrow B). For maximal stabilization of the positive charge in B, the carbon-silicon σ bond and the vacant p orbital must reside in a common plane. Intermediate B thus isomerizes, through a 60° bond rotation, to intermediate C. It is important to note that a 120° bond rotation in the opposite direction is disfavored because the carbon-silicon bond would have to rotate through a conformation in which the carbon-silicon σ bond and the vacant p orbital are perpendicular. The stabilizing overlap between the vacant p orbital and the carbon-silicon σ bond in C induces facile cleavage of the carbon-silicon bond to give vinyl iodide **181**.

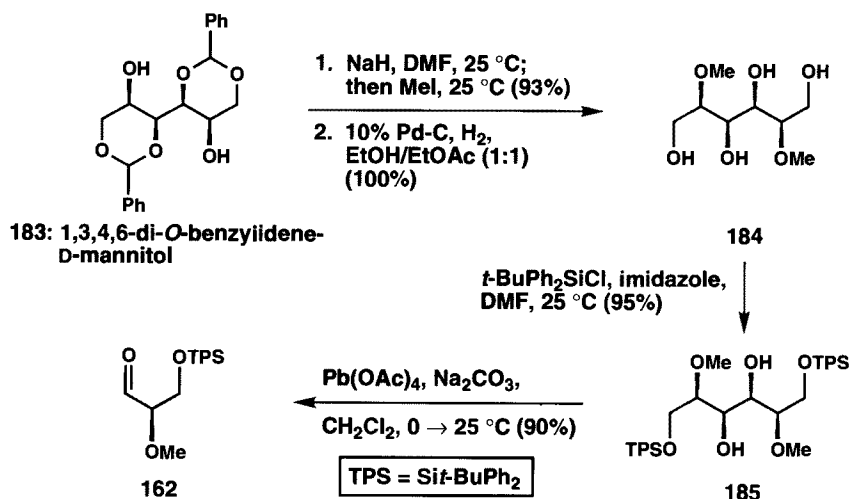
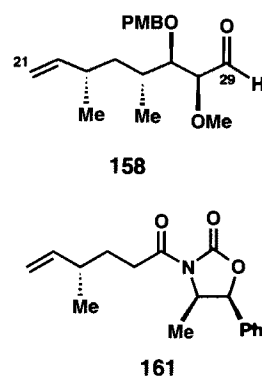
With the iodine atom in its proper place, provisions for construction of the C9-C10 bond by an aldol reaction could be made (see Scheme 44). To this end, oxidative cleavage of the *para*-methoxybenzyl ether in **181** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 - H_2O furnishes a primary alcohol that can



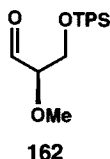
Scheme 44. Synthesis of the C8-C18 fragment **147**.

be oxidized to aldehyde **150** using the Swern procedure. It is, at this juncture, instructive to recall that carbons 9 and 10 of fragment **147** are destined to become part of carbonyl groups. As a result, it is not necessary to define the configurations of these two hydroxyl-bearing carbons. An intermolecular aldol condensation between aldehyde **150** and a simple glycolate enolate would thus constitute an acceptable solution to the problem at hand, and it would not matter if the union proceeded nonstereoselectively. In the event, reaction of aldehyde **150** with the dianion of methyl glycolate in a mixture of THF and HMPA at -78°C provides the expected mixture of diastereomeric aldol adducts (see **182**) (72% total yield). Alkaline hydrolysis of the terminal methyl ester group in **182** proceeds smoothly (95% yield) and completes the synthesis of the C8–C18 fragment **147**.

We now turn our attention to the C21–C28 fragment **158**. Our retrosynthetic analysis of **158** (see Scheme 42) identifies an expedient synthetic pathway that features the union of two chiral pool derived building blocks (**161**+**162**) through an Evans asymmetric aldol reaction. Aldehyde **162**, the projected electrophile for the aldol reaction, can be crafted in enantiomerically pure form from commercially available 1,3,4,6-di-*O*-benzylidene-*D*-mannitol (**183**) (see Scheme 45). As anticipated, the two free hydroxyls in the latter substance are methylated smoothly upon exposure to several equivalents each of sodium hydride and methyl iodide. Tetraol **184** can then be revealed after hydrogenolysis of both benzylidene acetals.

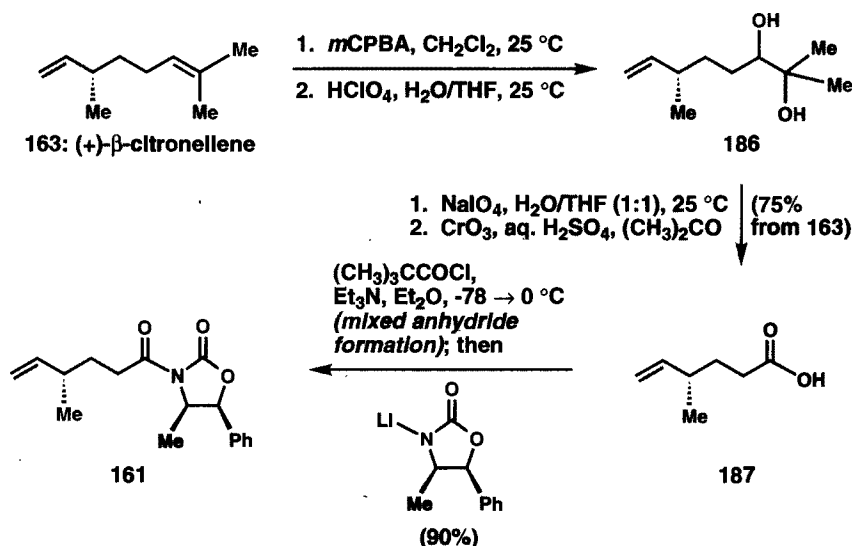


Scheme 45. Synthesis of aldehyde **162**.



the form of *tert*-butyldiphenylsilyl ethers with *tert*-butyldiphenylsilyl chloride (2.2 equiv.) and imidazole (4.5 equiv.) (**184** \rightarrow **185**). Finally, oxidative cleavage of the vicinal diol **185** with lead tetraacetate furnishes aldehyde **162** in 90 % yield.

An equally straightforward sequence can be used to fashion *N*-acyloxazolidinone **161** from commercially available (+)- β -citronellene (**163**) (see Scheme 46). Although **163** possesses two oxidizable sites of unsaturation, the trisubstituted olefin is more electron rich and thus more susceptible to oxidation by an electron deficient oxidant than the monosubstituted olefin. A selective epoxidation of the trisubstituted olefin in **163** can indeed be brought about with *meta*-chloroperoxybenzoic acid (*m*CPBA). Acid-catalyzed hydrolysis of the newly formed oxirane ring then furnishes vicinal diol **186**. Sodium periodate induced oxidative cleavage of **186**, followed by Jones oxidation of the resulting aldehyde, provides unsaturated carboxylic acid **187** in good overall yield. This four-step conversion of (+)- β -citronellene (**163**) to carboxylic acid **187** was developed by D.R. Williams et al.,⁷⁶ and it can be conducted easily without the isolation and purification of intermediates. On treatment with pivaloyl chloride and triethylamine, carboxylic acid **187** is converted to a mixed pivaloate anhydride, a reactive acylating agent that combines smoothly with the lithiated oxazolidinone derived from (1*S*,2*R*)-norephedrine to give *N*-acyloxazolidinone **161** (90 % overall yield).



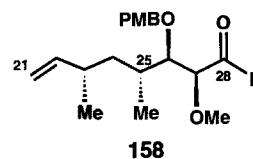
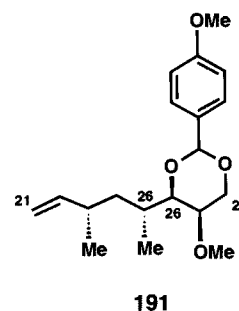
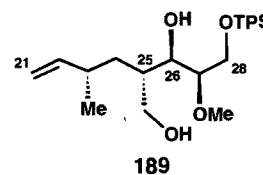
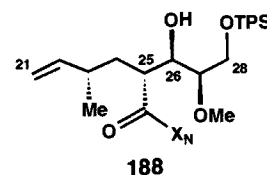
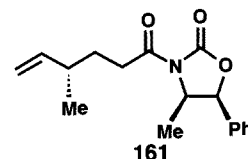
Scheme 46. Synthesis of *N*-acyloxazolidinone **161**.

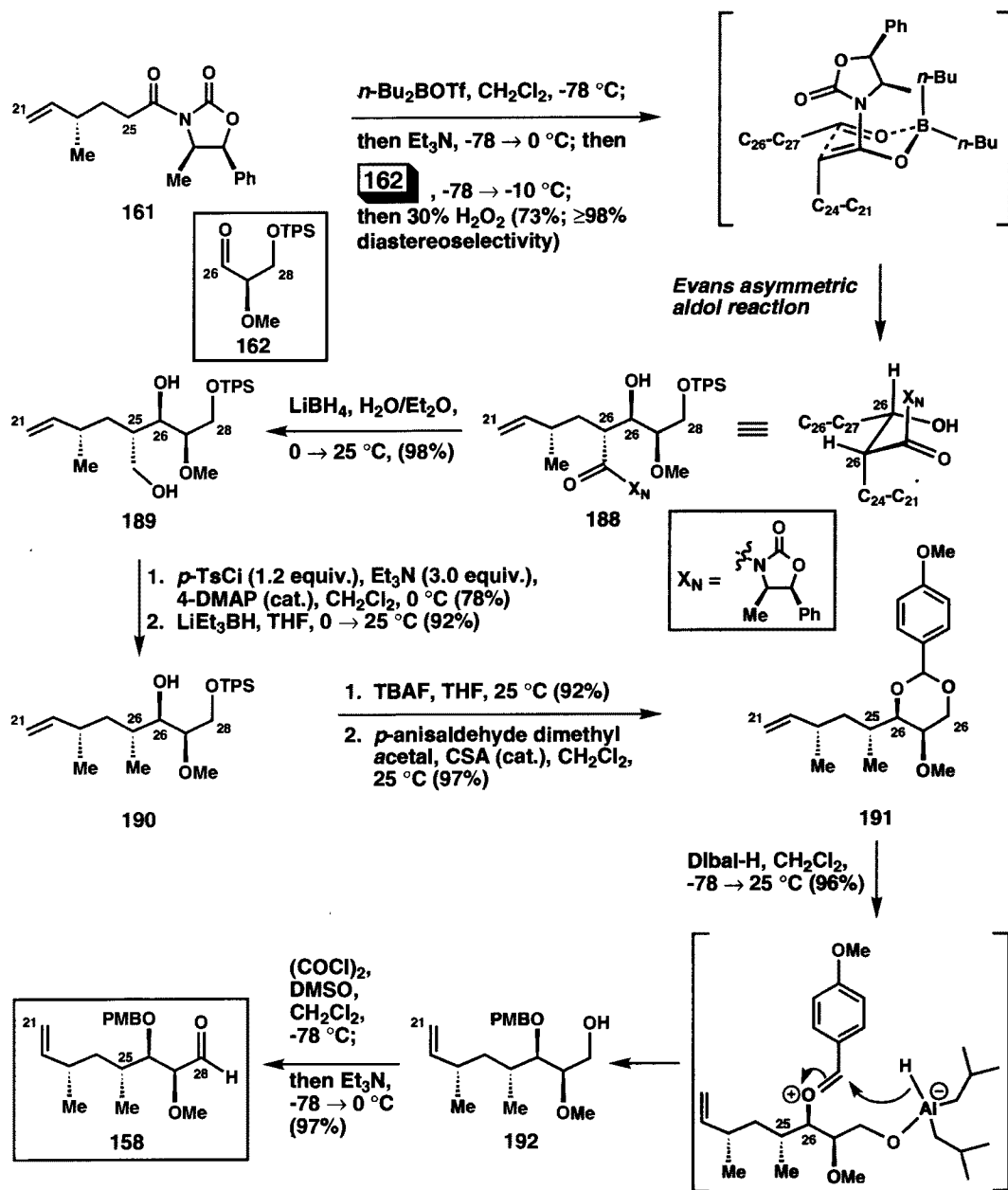
A valuable feature of the Evans asymmetric aldol process is that the stereoselectivity of the reaction is, with few exceptions, completely controlled by the oxazolidinone chiral auxiliary of the enolate component. Even in cases where the stereofacial preference of a chiral aldehyde opposes that of the chiral enolate, the latter usually prevails and dictates the stereochemical course of the aldol reaction. The Evans asymmetric aldol reaction is a powerful tool for the reagent-control strategy for achieving stereochemical control because the stereodirecting influence of the oxazolidinone chiral auxiliary can override the comparatively modest diastereofacial preference of a chiral aldehyde.⁷⁷ It was thus on the basis of substantial precedent that we invested much confidence in the proposition that the stereochemical course of an Evans aldol reaction employing **161** and **162** would be controlled by the norephedrine-derived chiral auxiliary (see Scheme 47). In the event, treatment of **161** with di-*n*-butylboron triflate and triethylamine furnishes a (*Z*)-boron enolate⁶⁹ that reacts stereoselectively with chiral aldehyde **162** in CH₂Cl₂ at -78 → 0 °C, affording *syn* aldol adduct **188** after workup with hydrogen peroxide (73 % yield; ≥ 98 % diastereoselectivity). This asymmetric aldol reaction defines the absolute stereochemistry at carbons 25 and 26.

Having served its purpose as a stereocontrolling device, the chiral auxiliary in aldol adduct **188** must be removed. At this stage, it is necessary to bring about the conversion of the carboximide moiety in **188** to the corresponding methyl group. To this end, subsection of **188** to the action of lithium borohydride accomplishes a reductive cleavage of the chiral imide function, furnishing 1,3-diol **189** in 98 % yield. By virtue of its less hindered nature, the primary hydroxyl group in **189** can be selectively converted to the corresponding *para*-toluenesulfonate ester with *para*-toluenesulfonyl chloride (1.2 equiv.) and triethylamine (78 % yield). The desired C-25 methyl group can then be generated upon exposure of the monotosylate to lithium triethylborohydride (super hydride) (92 % yield) leading to **190**.

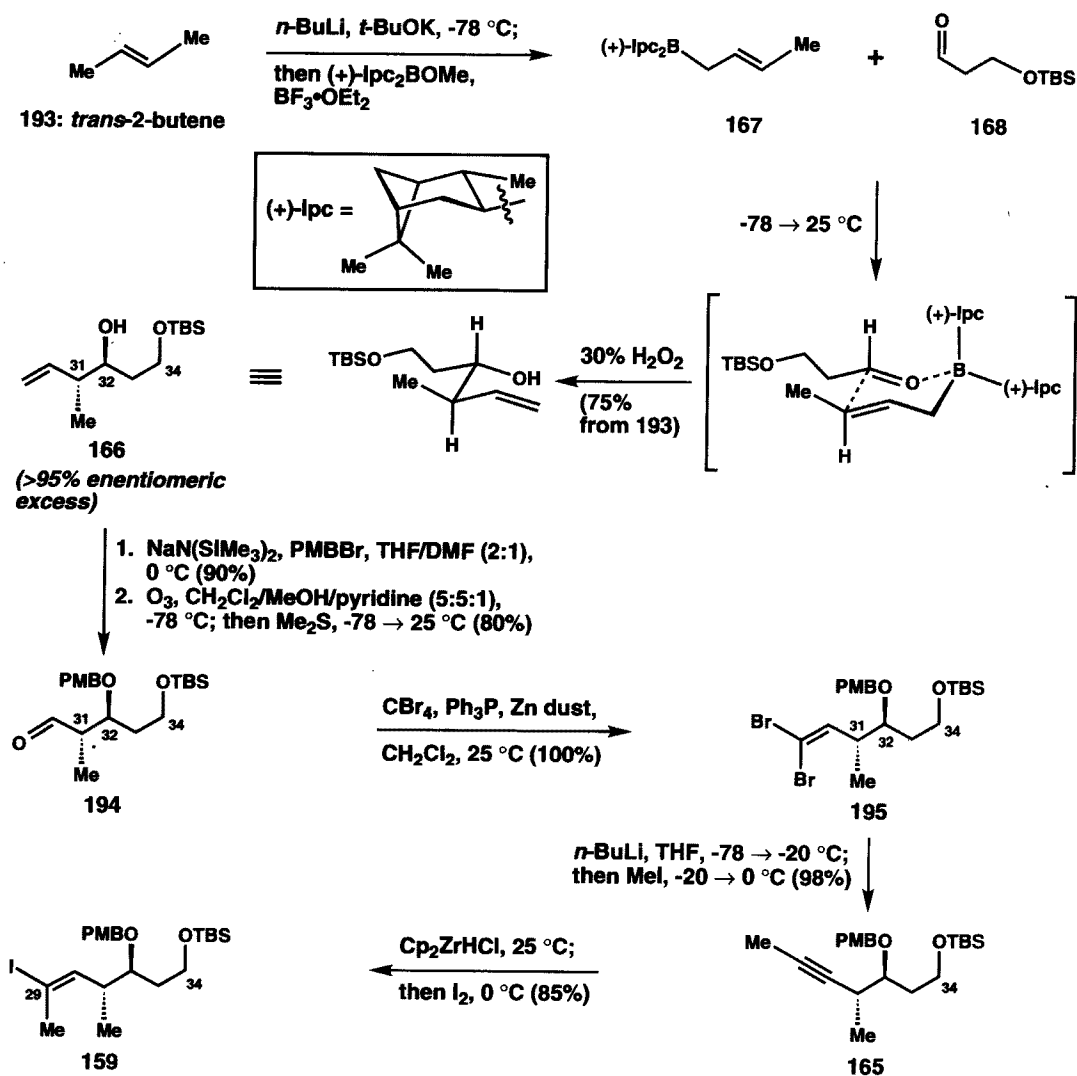
From alcohol **190**, the construction of the C21–C28 fragment **158** only requires a few functional group manipulations. Fluoride-induced cleavage of the *tert*-butyldiphenylsilyl ether in **190** furnishes a diol that reacts smoothly with *para*-anisaldehyde dimethyl acetal in the presence of a catalytic amount of CSA to give benzylidene acetal **191** (89 % yield from **190**). Interestingly, when a solution of **191** in CH₂Cl₂ is exposed at -78 °C to the Lewis-acidic reducing agent diisobutylaluminum hydride (Dibal-H), followed by warming to 25 °C, a regioselective reductive cleavage of the benzylidene acetal takes place to give primary alcohol **192** (96 % yield).^{66,78} A Swern oxidation of the latter substance completes the synthesis of fragment **158**.

The C29–C34 fragment, *trans* vinyl iodide **159**, is distinguished by two contiguous stereogenic centers, and it was surmised that both could be introduced in a single step through the application of Brown's effective asymmetric crotylboration methodology (see Scheme 48).⁷⁹ Depro-

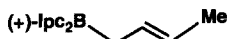




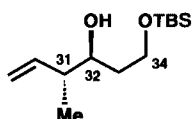
Scheme 47. Synthesis of the C21–C28 fragment 158.



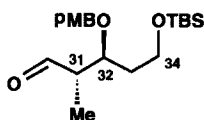
Scheme 48. Synthesis of the C29–C34 fragment 159.



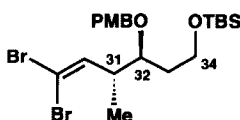
167



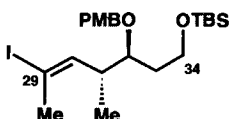
166



194



195



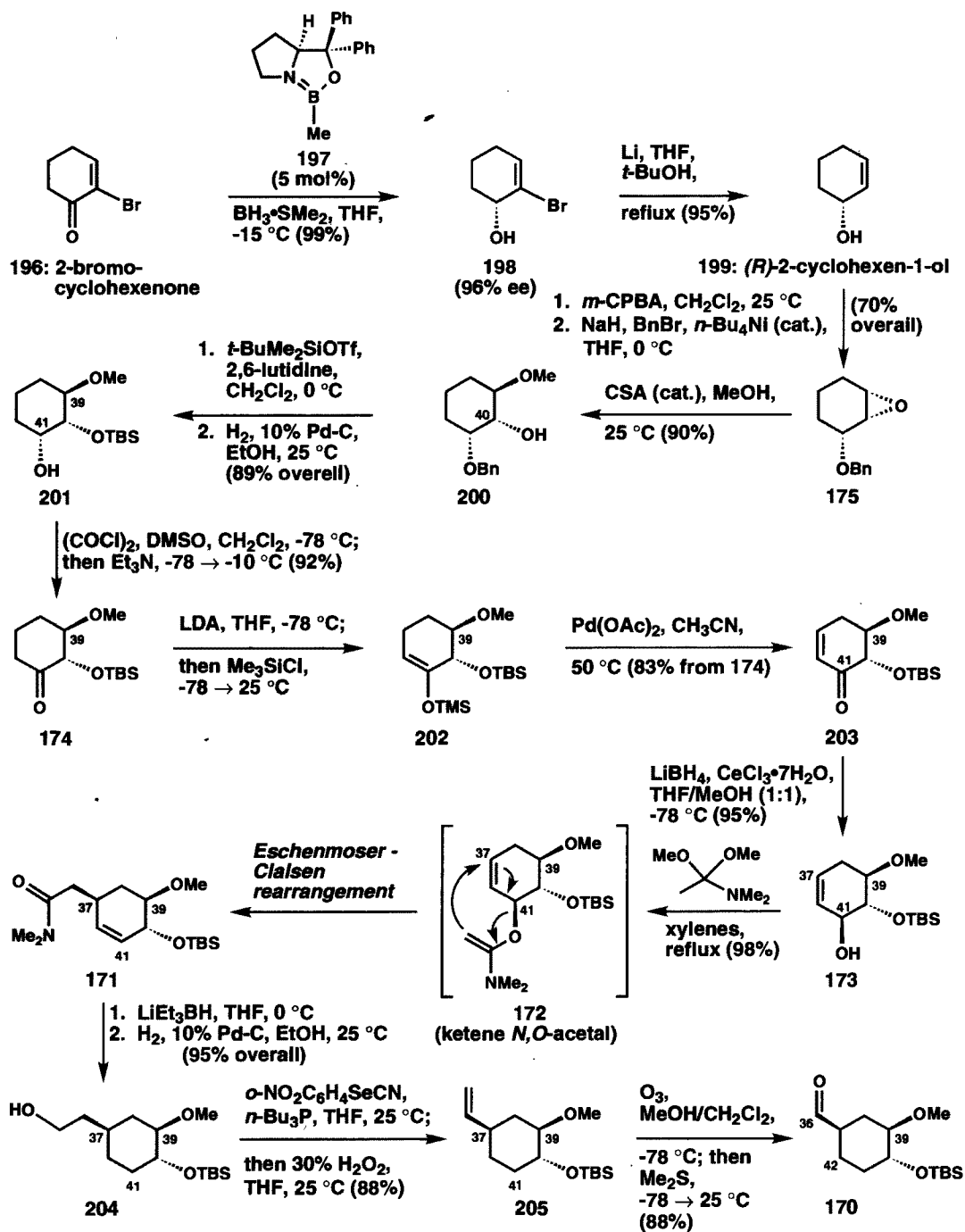
159

tonation of *trans*-2-butene (**193**) using Schlosser's super base procedure (*n*-BuLi + *t*-BuOK),⁸⁰ followed by reaction of the resulting anion with (+)-Ipc₂BOMe and BF₃•OEt₂, produces chiral boron reagent **167**. When the latter is exposed to achiral aldehyde **168**, an asymmetric crotylboration reaction takes place, affording optically active secondary alcohol **166** (>95 % enantiomeric excess) after workup (75 % overall yield). This intermolecular union establishes the requisite C31/C32 stereorelationship and can be conducted on large scale.

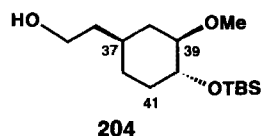
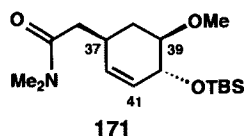
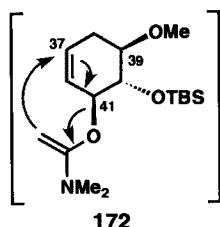
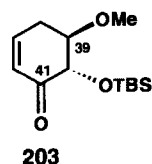
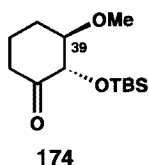
Having introduced the two unsymmetrically substituted carbon atoms, we then needed to convert **166** into a form amenable to the introduction of the conspicuous *trans* vinyl iodide grouping. Since a free secondary hydroxyl group would not be compatible with some of the operations that we planned, it was necessary to protect the hydroxyl group attached to C-32 in **166**. To this end, exposure of alcohol **166** to sodium bis(trimethylsilyl)amide [NaN(SiMe₃)₂] and *para*-methoxybenzylbromide (PMBBr) results in the formation of the corresponding *para*-methoxybenzyl ether (90 % yield). Aldehyde **194**, revealed upon ozonolytic cleavage of the terminal C–C double bond, undergoes quantitative conversion to dibromo olefin **195** on treatment with carbon tetrabromide, triphenylphosphine, and zinc dust.⁸¹ In the presence of 2.1 equivalents of *n*-butyllithium, compound **195** participates in sequential dehydrobromination and halogen–lithium exchange reactions, affording a lithium acetylide that reacts efficiently with methyl iodide to give alkyne **165** (98 % yield). A regioselective *syn* addition of the Zr–H bond of Schwartz's reagent to the alkyne function in **165** produces, after quenching with iodine, *trans* vinyl iodide **159** (85 % yield).⁸²

The synthesis of the trisubstituted cyclohexane sector **160** commences with the preparation of optically active (*R*)-2-cyclohexen-1-ol (**199**) (see Scheme 49). To accomplish this objective, the decision was made to utilize the powerful catalytic asymmetric reduction process developed by Corey and his colleagues at Harvard.⁸³ Treatment of 2-bromocyclohexenone (**196**) with BH₃•SMe₂ in the presence of 5 mol % of oxazaborolidine **197** provides enantiomerically enriched allylic alcohol **198** (99 % yield, 96 % *ee*). Reductive cleavage of the C–Br bond in **198** with lithium metal in *tert*-butyl alcohol and THF then provides optically active (*R*)-2-cyclohexen-1-ol (**199**). When the latter substance is treated with *m*CPBA, a hydroxyl-directed Henbest epoxidation⁸⁴ takes place to give an epoxy alcohol which can subsequently be protected in the form of a benzyl ether (see **175**) under standard conditions.

The oxirane ring in **175** is a valuable function because it provides a means for the introduction of the β -disposed C-39 methoxy group of rapamycin. Indeed, addition of CSA (0.2 equivalents) to a solution of epoxy benzyl ether **175** in methanol brings about a completely regioselective and stereospecific solvolysis of the oxirane ring, furnishing the desired hydroxy methyl ether **200** in 90 % yield. After protection of the newly formed C-40 hydroxyl in the form of a *tert*-butyldimethylsilyl (TBS) ether, hydrogenolysis of the benzyl ether provides alcohol **201** in 89 % overall yield.



Scheme 49. Synthesis of aldehyde 170.

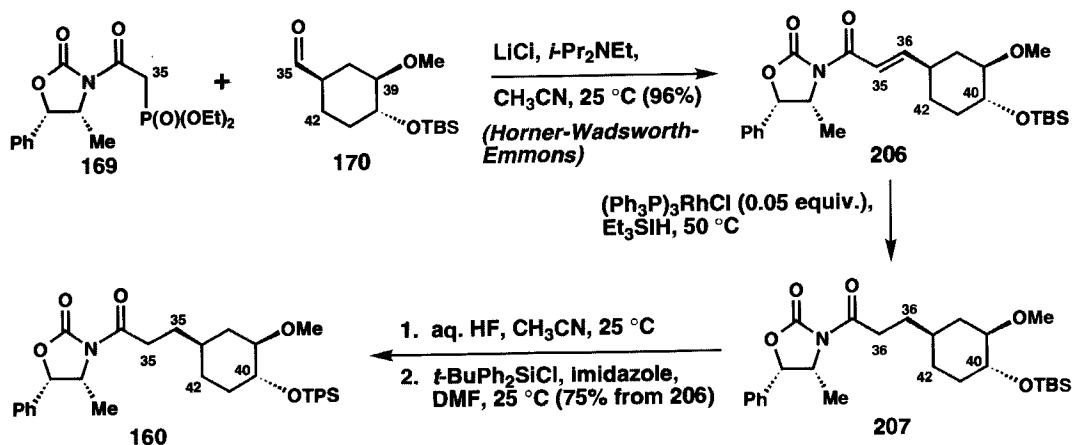


To set the stage for the crucial Eschenmoser–Claisen rearrangement, it is necessary to introduce unsaturation into the six-membered ring and invert the configuration of the hydroxyl-bearing C-41 stereocenter. Both of these tasks can be mastered straightforwardly. Thus, ketone **174**, the product of a Swern oxidation of alcohol **201**, can be converted into the corresponding kinetic enolate by treatment with lithium diisopropylamide (LDA), and thence to silyl enol ether **202** by trimethylsilylation of the enolate oxygen. Oxidation of the latter substance with palladium(II) acetate in acetonitrile at 50 °C⁸⁵ introduces the requisite C–C double bond, affording enone **203** in 83 % yield from **202**. At this stage, it was hoped that the desired equatorial C-41 hydroxyl group could be introduced through axial delivery of hydride to the C-41 ketone carbonyl in **203**. Gratifyingly, 1,2-reduction of enone **203** by lithium borohydride in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ ⁸⁶ proceeds diastereoselectively and provides allylic alcohol **173** in 95 % yield.

Having established the C-41 hydroxyl-bearing stereocenter as shown in **173**, we were confident that the C-37 appendage could be introduced by way of a stereospecific [3,3] sigmatropic rearrangement. Although one of many Claisen rearrangement variants could have been selected to accomplish the desired [3,3] sigmatropic shift,⁸⁷ we chose the Eschenmoser variant.⁷² In the event, when allylic alcohol **173** is reacted with *N,N*-dimethylacetamide dimethyl acetal in refluxing xylenes, it undergoes conversion to ketene *N,O*-acetal **172** and thence to γ,δ -unsaturated amide **171** by an Eschenmoser–Claisen rearrangement; this stereospecific [3,3] sigmatropic rearrangement accomplishes the formation of a key C–C bond and a 1,3-transfer of stereochemistry from C-41 to C-37.

Although the newly fashioned side chain attached to C-37 in **171** is oriented correctly relative to the other two ring substituents, it has one carbon too many. A synthesis of aldehyde **170** from amide **171** (see Scheme 49) requires the removal of this extra carbon atom. Of the various multistep sequences that one could consider for the conversion of **171** to **170**, we found the pathway shown in Scheme 49 to be reasonably efficient. This four-step sequence is initiated by a complete reduction of the *N,N*-dimethylamide function in **171** to the corresponding primary alcohol with superhydride. Hydrogenation of the ring double bond then gives alcohol **204** (95 % overall yield). Subjection of **204** to Grieco's *ortho*-nitrophenylselenenylation procedure⁸⁸ affords, after oxidative *syn*-elimination, alkene **205** (86 % yield). Finally, ozonolysis of the C–C double bond in **205** reveals the targeted aldehyde **170**. Although the susceptibility of **170** to epimerization at C-37 was cause for some concern, it should be noted that all three of the substituents in **170** can adopt favorable equatorial positions.

Aldehyde **170** is to serve as the electrophile in an intermolecular Horner–Wadsworth–Emmons (HWE) reaction⁷⁰ with enantiomerically pure phosphonate **169**. Compounds **169** and **170** can in fact be joined efficiently under the mild reaction conditions shown in Scheme 50 to give α,β -unsaturated imide **206** (96 % yield). The use



Scheme 50. Synthesis of the C35–C42 fragment **160**.

of lithium chloride and a mild amine base such as diisopropylethylamine (Hünig's base) to bring about the union of phosphonates and aldehydes was developed by Masamune and Roush.⁸⁹ A virtue of this mild method is that base-sensitive aldehydes and phosphonates can be coupled smoothly without competing epimerizations and/or other destructive reaction processes. In the HWE coupling of **169** and **170**, it is presumed that the Lewis-acidic lithium cation coordinates both the imide carbonyl and the phosphonate oxygen in **169**, thereby lowering the pK_a of the C-35 α -methylene hydrogens. A mild amine base can therefore be used to effect the necessary phosphonate deprotonation. Complexation of the Lewis-basic carbonyl oxygen in **170** by Li^+ is also important because it enhances the electrophilic character of the C-36 carbonyl carbon and facilitates the nucleophilic addition step.

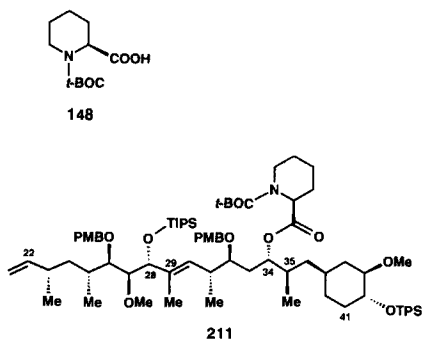
When **206** is exposed to the action of triethylsilane and a catalytic amount of tris(triphenylphosphine)rhodium chloride $[(\text{Ph}_3\text{P})_3\text{RhCl}]$, the $\Delta^{35,36}$ double bond is saturated and compound **207** is produced. Unfortunately, subsequent operations dictated the exchange of the *tert*-butyldimethylsilyl protecting group for the more robust *tert*-butyldiphenylsilyl (TPS) protecting group at this stage. This objective is easily achieved by fluoride-induced cleavage of the C-40 *tert*-butyldimethylsilyl (TBS) ether in **207**, followed by *tert*-butyldiphenylsilylation of the resulting C-40 alcohol. In this manner, building block **160** can be prepared in 75 % overall yield from unsaturated imide **206**.

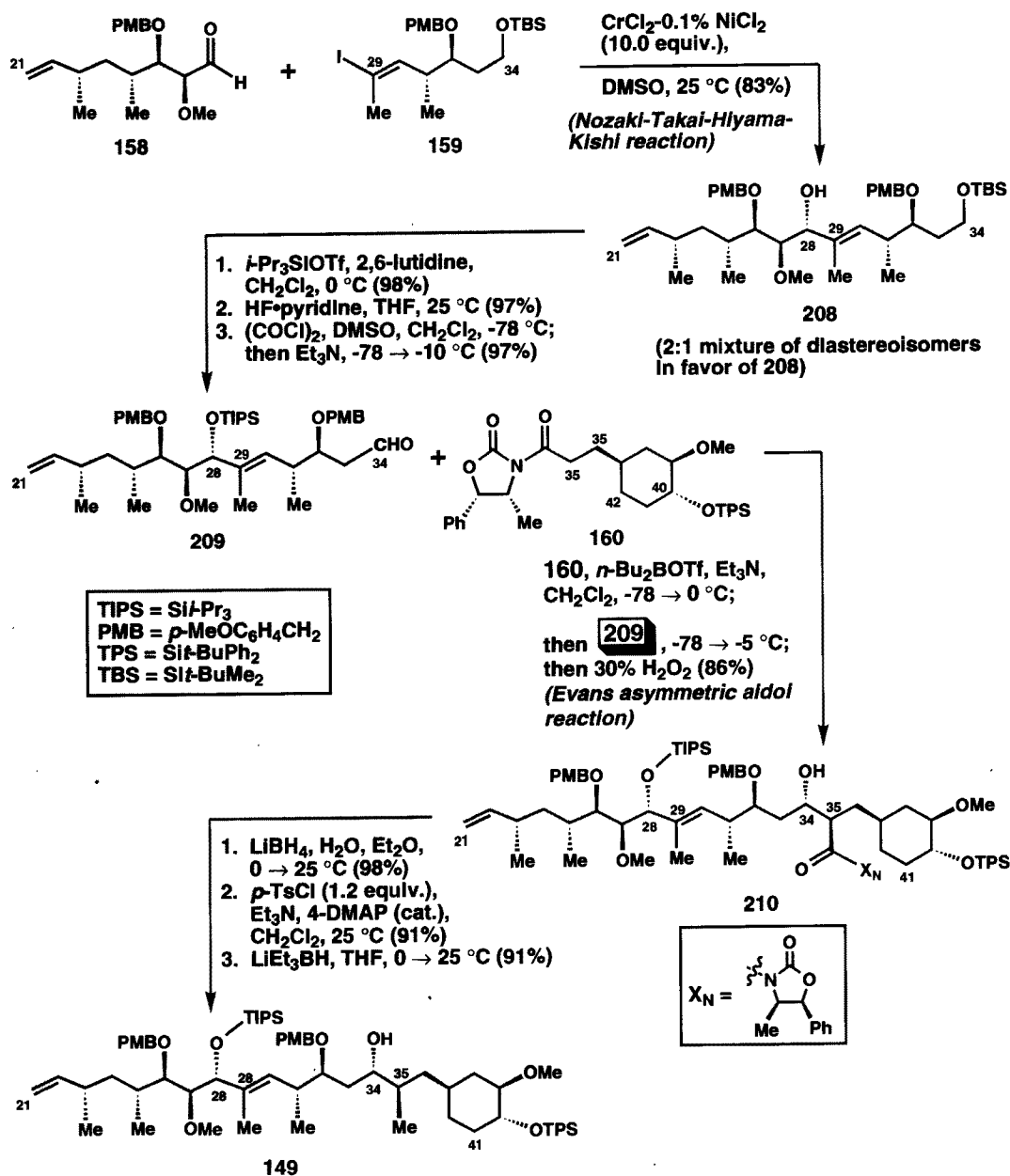
31.3.2 Coupling of Key Intermediates **147** and **158–160**

The coupling of compounds **158** and **159** can be achieved by a Nozaki–Takai–Hiyama–Kishi reaction⁶⁸ as shown in Scheme 51. Thus, treatment of a mixture of **158** and **159** in DMSO with chromium(II) chloride containing 0.1 % nickel(II) chloride at 25 °C furnishes a 2:1 mixture of allylic alcohol diastereoisomers in favor of the desired compound **208** (83 % total yield). Although the degree of diastereoselectivity is poor, the epimeric allylic alcohols can be separated chromatographically, and the undesired C-28 epimer can be converted to compound **208** by an oxidation–reduction sequence. In preparation for the second coupling, the C-28 hydroxyl in **208** is protected in the form of a triisopropylsilyl ether with triisopropylsilyl triflate and 2,6-lutidine (98 % yield). After selective fluoride-induced cleavage of the *tert*-butyldimethylsilyl ether, a Swern oxidation of the resultant primary alcohol provides aldehyde **209** (94 % yield for two steps). As planned, aldehyde **209** combines smoothly with the (*Z*)-boron enolate derived from the C35–C42 fragment **160** to give *syn* aldol adduct **210** in 86 % yield. This convergent Evans asymmetric aldol reaction establishes the necessary stereochemical relationships at C-34 and C-35, and it is noteworthy that compound **210** is the only aldol adduct observed.

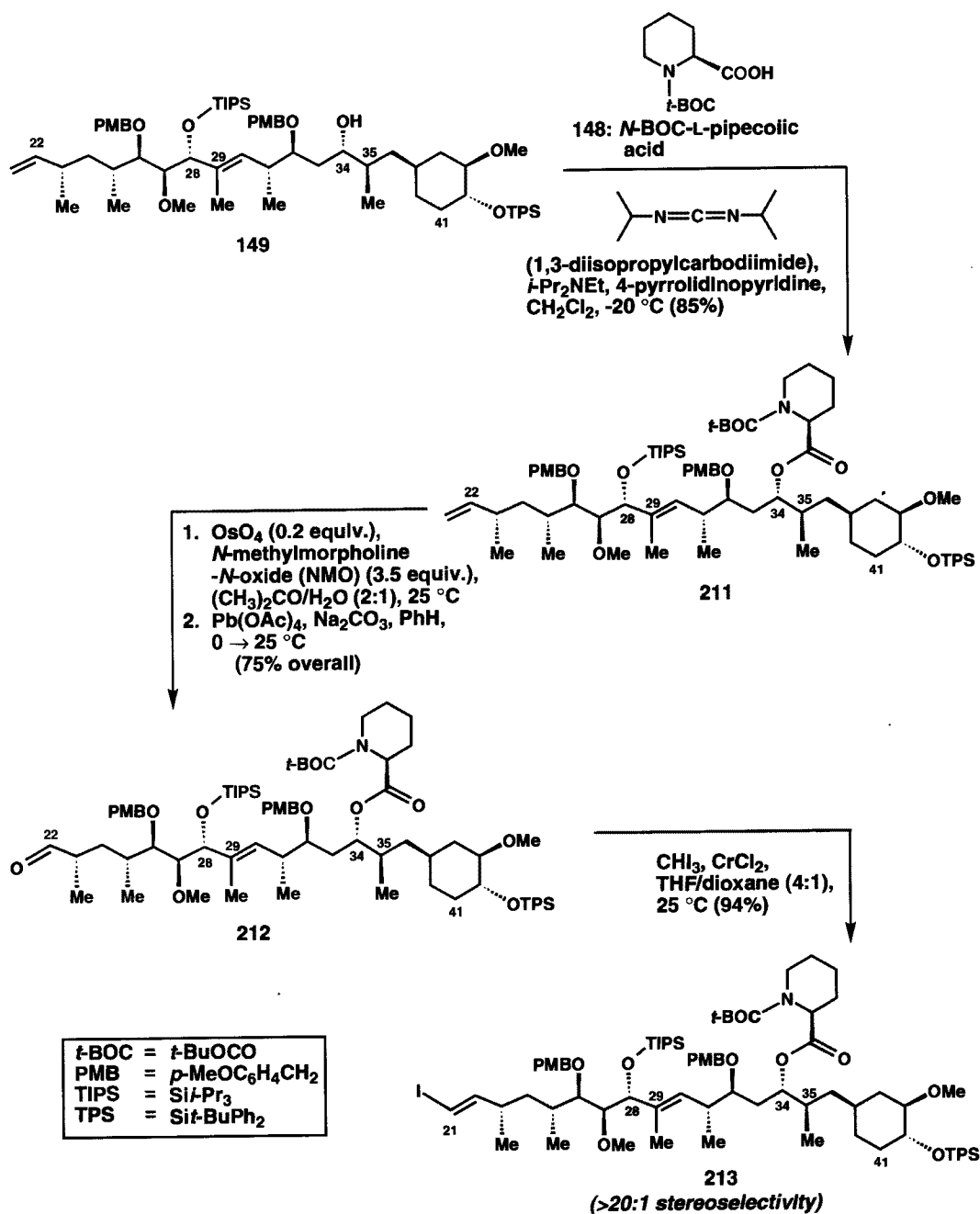
The chiral oxazolidinone auxiliary in **210**, which had served so well in its capacity as a stereocontrolling device, must, at this stage, be removed from the molecule. To advance further into the synthesis, it would be necessary to reduce the carboximide moiety in **210** completely (i.e. to the corresponding methyl group), and it will be recalled that this type of transformation had already been accomplished during the course of the synthesis of fragment **158** (see **188** → **189** → **190**, Scheme 47). Gratifyingly, the same three-step reaction sequence that permitted the carboximide → methyl group transformation in the synthesis of **158** is also successful in this context. Thus, exposure of carboximide **210** to lithium borohydride gives rise to a 1,3-diol, the primary hydroxyl group of which can be selectively derivatized with *para*-toluenesulfonyl chloride. The desired C-35 methyl group can then be generated upon reduction of the monosulfonate ester with lithium triethylborohydride (super hydride).

Two reliable bond constructions – a Nozaki–Takai–Hiyama–Kishi reaction and an Evans asymmetric aldol reaction – have allowed the union of three advanced, optically active building blocks. The introduction of the remaining C8–C18 fragment, compound **147**, would follow the attachment of the L-pipecolic acid residue to intermediate **149** (see Scheme 52). In the presence of 1,3-diisopropylcarbodiimide, Hünig's base, and 4-pyrrolidino-pyridine, *N*-*t*-BOC-L-pipecolic acid (**148**) undergoes conversion to a reactive acylating agent, presumably an *O*-acylisourea, which reacts with alcohol **149** to give ester **211** (85 % yield). A selective dihydroxylation of the less hindered terminal double bond in **211** using a catalytic amount of osmium tetroxide and stoichiometric

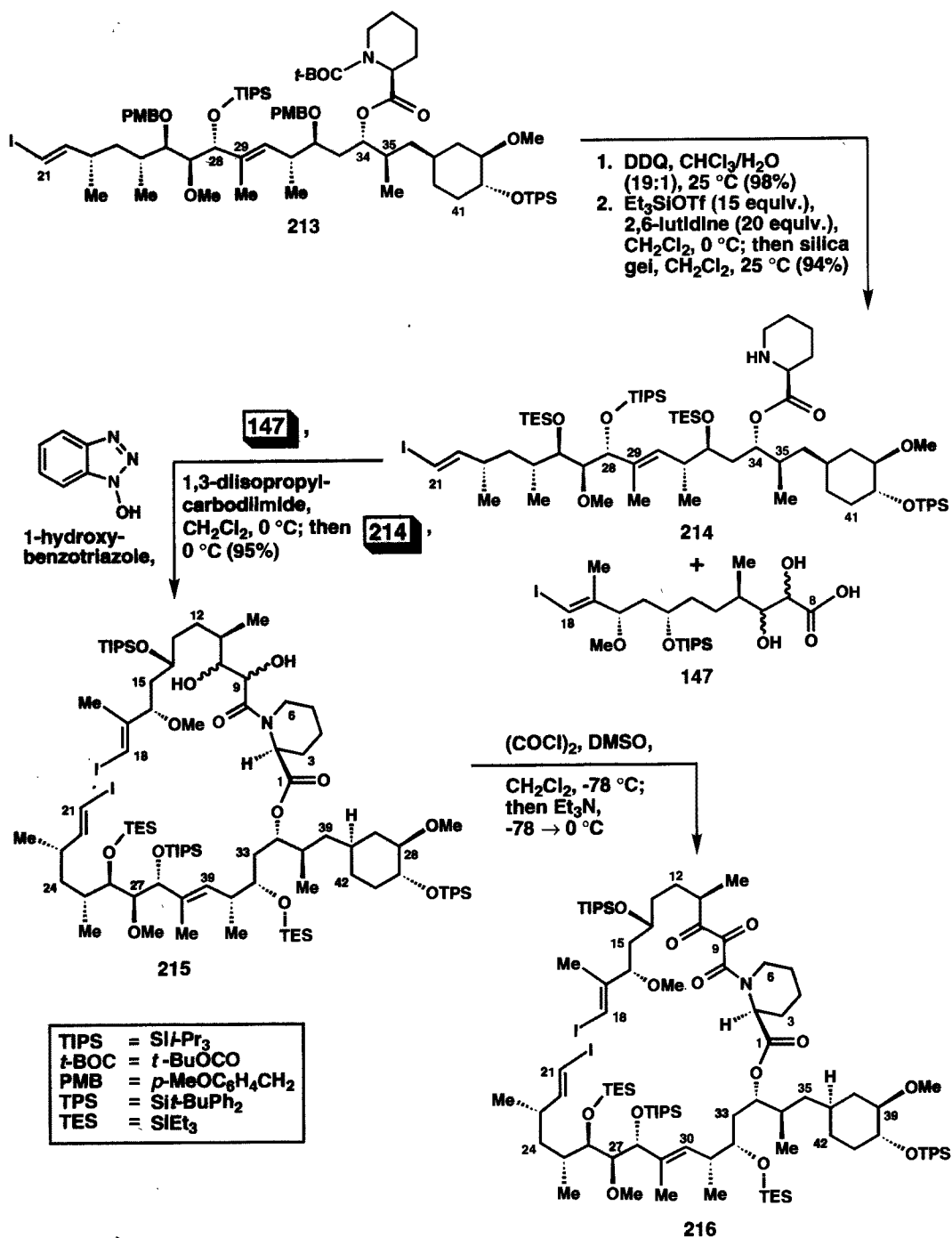




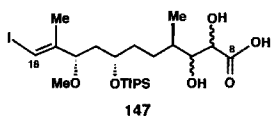
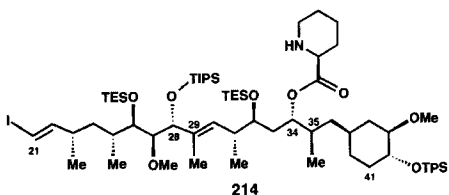
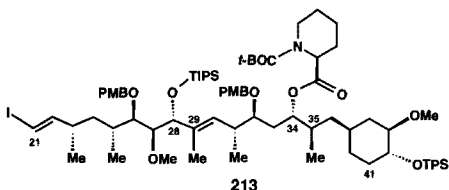
Scheme 51. Synthesis of the C21-C42 fragment 149.



Scheme 52. Synthesis of intermediate 213.



Scheme 53. Synthesis of intermediate 216.

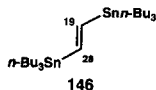
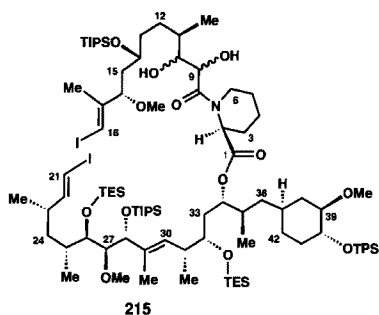


amounts of *N*-methylmorpholine-*N*-oxide (NMO) (the “Upjohn” process),⁹⁰ followed by Pb(OAc)₄-induced oxidative cleavage of the intermediate diol, provides aldehyde **212** in 75 % overall yield. When the latter compound is subjected to Takai’s CrCl₂-mediated iodoolefination process,^{68f,91} the desired *trans* vinyl iodide **213** is produced in >20:1 stereoselectivity and in excellent yield.

It was considered prudent at this stage to replace the *para*-methoxybenzyl ethers in **213** with silicon protecting groups that could be removed easily at a subsequent stage with fluoride ion. As expected, the action of DDQ in CHCl₃/H₂O (19:1) on **213** causes oxidative cleavage of both *para*-methoxybenzyl ethers (Scheme 53). The resulting diol can then be converted to compound **214** on treatment with excess quantities of triethylsilyl triflate and 2,6-lutidine, followed by exposure of the crude product to silica gel in CH₂Cl₂. In this transformation, the two hydroxyl groups, liberated by the action of DDQ on **213**, are protected in the form of triethylsilyl ethers, and the *tert*-butyl carbamate (*t*-BOC) is cleaved.^{65a,92} Treatment of the crude product with a slurry of silica gel in CH₂Cl₂ causes decomposition of the triethylsilyl carbamate and affords the free amine **214** (92 % yield from **213**).

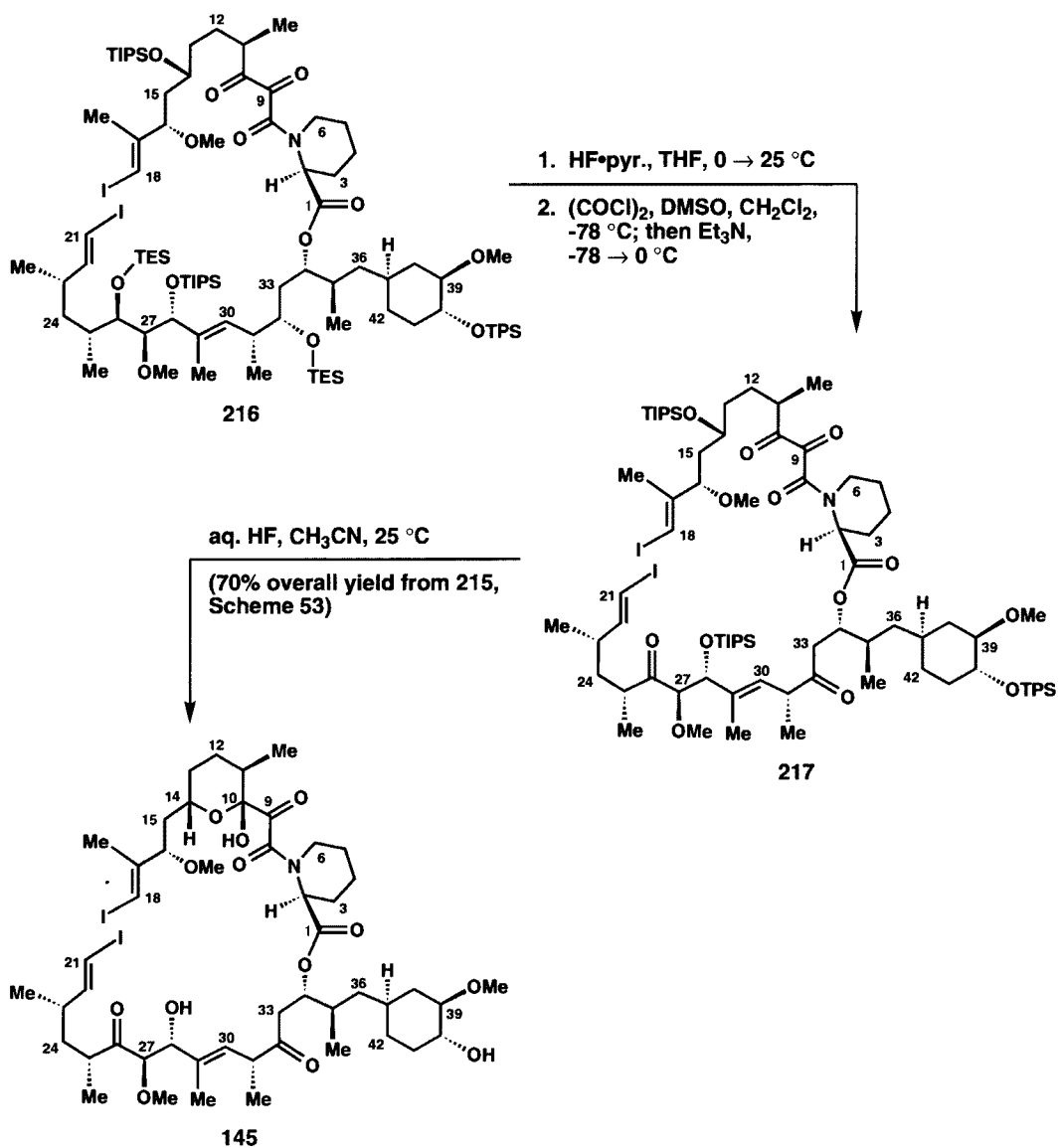
It was anticipated that fragments **147** and **214** could be united through an amide bond linking the nitrogen atom of the latter with C-8 of the former. Indeed, the active ester formed by treatment of carboxylic acid **147** with 1,3-diisopropylcarbodiimide and 1-hydroxybenzotriazole reacts efficiently with amine **214** to afford dihydroxy amide **215** in 95 % yield. This convergent union creates a molecule that possesses all but two carbon atoms of the natural product.

31.3.3 Final Stages and Cyclization to Rapamycin



Our strategy is based on the premise that the 31-membered ring and the conjugated triene array of the natural product could be fashioned simultaneously by a tandem inter-/intramolecular Stille coupling. Moreover, the mild conditions under which Stille couplings can be performed fueled hopes that the crucial “stitching cyclization” could be conducted on a fully deprotected seco bis(vinyl iodide) (see **145**, Schemes 40 and 54); the “stitching cyclization” would thus be the final operation in the synthesis.

Prior to the twofold Stille coupling with *trans*-1,2-bis-(tri-*n*-butylstannyl)ethylene (**146**), the long-chain bis(vinyl iodide) **215** must be appropriately manipulated in order to bring it to the correct oxidation state and rigidify it. Through the use of the Swern procedure, diol **215** (mixture of stereoisomers) can be oxidized to the vicinal tricarbonyl compound **216** (Scheme 53). Selective cleavage of the triethylsilyl ethers attached to C-26 and C-32 in compound **216** with HF•pyridine in THF, followed by Swern oxidation of the resulting diol, provides compound **217** in good yield (Scheme 54). Fluoride-induced removal of the remaining three silyl protecting

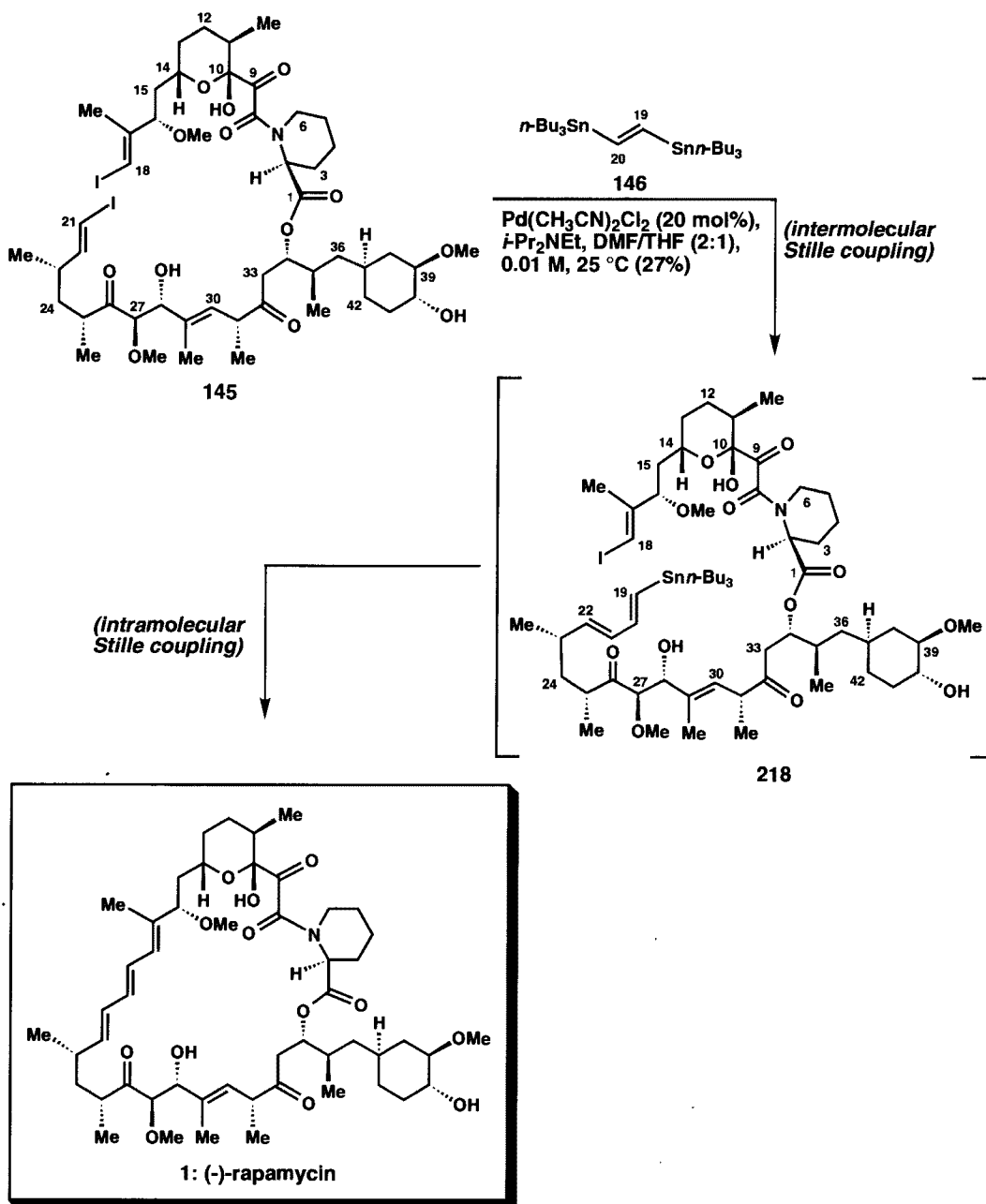
**Scheme 54.** Synthesis of intermediate 145.

groups, with concomitant formation of an internal hemiketal, affords compound **145** in 70 % overall yield from **215**. Compound **145** is produced as a mixture of two major diastereoisomers, presumed to be lactol epimers.

The stage is now set for an evaluation of the most crucial maneuver in the synthesis. Gratifyingly, the much anticipated reaction between bis(vinyl iodide) **145** and enedistannane **146** proceeds successfully in dilute DMF/THF (0.01 M) in the presence of Hünig's base and $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (20 mol %) at ambient temperature to afford (–)-rapamycin (**1**) in 27 % yield (Scheme 55). This productive transformation is presumably initiated by an intermolecular Stille coupling between **146** and the less hindered C-21 vinyl iodide terminus of **145** (see **145**+**146**→**218**, Scheme 55). A second Stille coupling, this time in an intramolecular fashion, establishes the C18–C19 bond and completes the total synthesis (see **218**→**1**). Unchanged starting material (ca. 30 % yield) and a vinyl iodide/vinylstannane intermediate (ca. 30 % yield), both of which can be recycled, were isolated from this tandem Stille reaction. Although its identity was not established, the vinyl iodide/vinylstannane intermediate was assumed to be **218**. In solution, synthetic rapamycin exists, just as natural rapamycin does, as a mixture of two major isomeric substances, presumably the six- and seven-membered ring lactols formed from the C-14 hydroxyl group and the C-10 and C-9 carbonyl groups, respectively. Synthetic rapamycin produced in this manner exhibited identical physical and spectroscopic properties to those of an authentic sample.

31.4 Conclusion

The first asymmetric total synthesis of rapamycin (**1**) described in this chapter is distinguished by a high degree of convergency. It is also distinctly direct in that the penultimate open-chain precursor, although highly functionalized, contains no protecting groups. The twofold Stille cyclization strategy ("stitching cyclization"), first developed during this synthesis, is already finding other applications in organic synthesis.^{93–95} Finally, by virtue of its flexibility, the synthetic strategy described herein is ideally suited for the construction of rapamycin analogs with potential applications in biology and medicine.

Scheme 55. Synthesis of (-)-rapamycin (**1**).

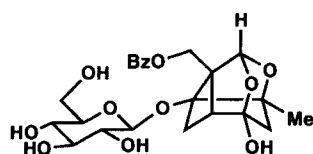
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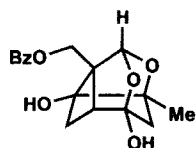
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1: paeoniflorin



2: paeoniflorigenin

E. J. Corey (1993)

Paeoniflorigenin and Paeoniflorin

32.1 Introduction

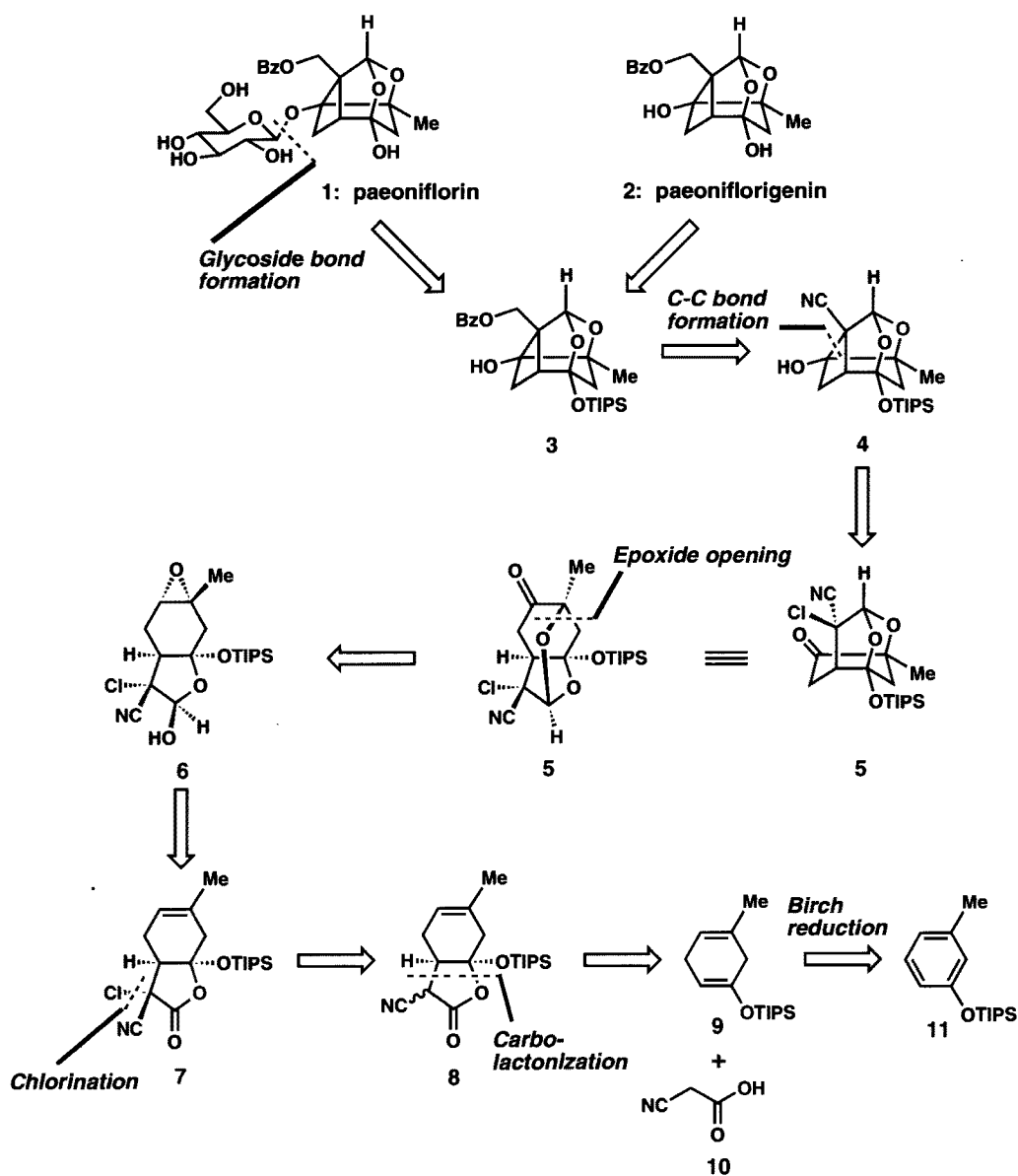
The root of the Chinese peony, *Paeonia lactiflora*, is the source of a structurally novel monoterpene that bears the name paeoniflorin (**1**).¹ Paeoniflorin exhibits sedative, anticoagulant, and anti-inflammatory activity, and it occupies an important place in traditional Chinese medicine.² The structure of **1** is very complex. Its strained, cage-like pinane framework is highly oxygenated and contains numerous stereogenic centers. In fact, with the exception of the β -glucose sugar and benzoate ester moieties, six of the remaining ten carbon atoms are tetrahedral and unsymmetrically substituted and one is quaternary. In this chapter, we address the elegant substrate-stereocontrolled total synthesis of paeoniflorin (**1**) and its aglycon, (\pm)-paeoniflorigenin [(\pm) -**2**], by E. J. Corey and his group at Harvard.³ The general features of Corey's synthesis of paeoniflorin and of paeoniflorigenin are presented in Scheme 1.

32.2 Retrosynthetic Analysis and Strategy

The homology between compounds **1** and **2** is obvious. Paeoniflorin (**1**) can be formed in the event that a β -glycosidation of a suitably protected derivative of paeoniflorigenin (**2**) can be achieved. Retrosynthetic cleavage (see Scheme 1) of the glycosidic bond in **1** furnishes intermediate **3** as a potential precursor and key synthetic

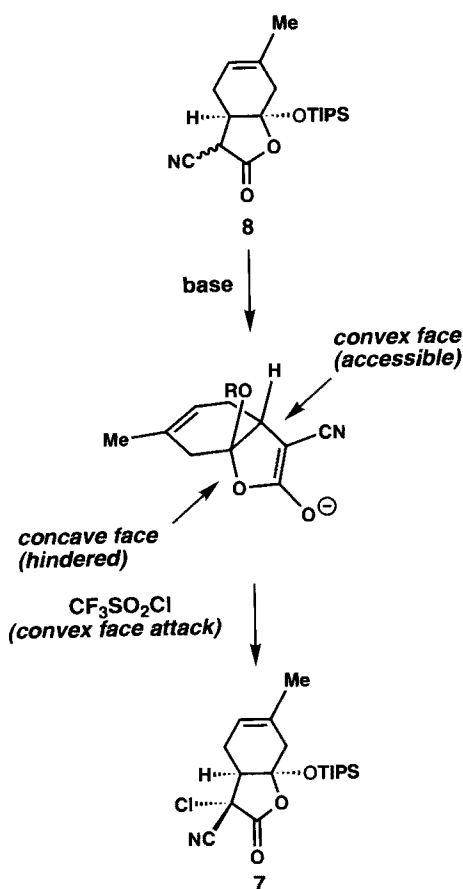
intermediate. In the forward sense, a β -selective glycosidation of the tertiary hydroxyl group in **3**, followed by deprotections, could furnish paeoniflorin (**1**), while cleavage of the triisopropylsilyl ether in **3** could give paeoniflorigenin (**2**). Through a straightforward sequence of functional group manipulations, **3** could be derived from intermediate **4**. Retrosynthetic cleavage of the indicated carbon-carbon bond in **4** dismantles the strained, four-membered ring, accomplishes significant structural simplification, and provides ketochloronitrile **5** as a potential precursor. A crucial transformation in this synthesis is the construction of the four-membered ring through a samarium(II)-mediated intramolecular Barbier reaction.⁴ In the synthetic direction, exposure of ketochloronitrile **5** to the action of the powerful reducing agent, samarium diiodide,⁵ is expected to accomplish reduction of the carbon-chlorine bond with concomitant cyclization to give **4**. In the context of intermediate **5**, the spatial proximity between the chlorine-bearing carbon and the ketone carbonyl would likely have a very favorable impact on the cyclization event. This clever intramolecular bond-forming process could achieve the simultaneous formation of the strained cyclobutane ring of paeoniflorigenin and two contiguous stereogenic centers.

Retrosynthetic disassembly of the ether bridge in **5** leads back to intermediate **6**. In the synthetic direction, suitable activation of the oxirane ring in **6** could conceivably initiate an internal etherification reaction to give, after an oxidation reaction, the oxa-bridged ketone **5**. Intermediate **6** could be derived in a straightforward manner from bicyclic lactone **7**. Epoxidation of the trisubstituted olefin in **7** and a partial reduction of the lactone carbonyl could secure the formation of **6** from **7**. Intermediate **8**, a viable precursor of **7**, could conceivably be fashioned in a very productive manner through a chemo- and regioselective Mn^{III}-mediated carbolactonization reaction between cyanoacetic acid (**10**) and dihydro-*meta*-cresol triisopropylsilyl ether (**9**), the product of a Birch reduction⁶ of the triisopropylsilyl ether of *meta*-cresol (**11**). Thus, through a seemingly straightforward sequence of reactions, paeoniflorigenin (**2**) and its close relative, paeoniflorin (**1**), could ultimately be derived from a modestly functionalized, planar aromatic compound (**11**)!

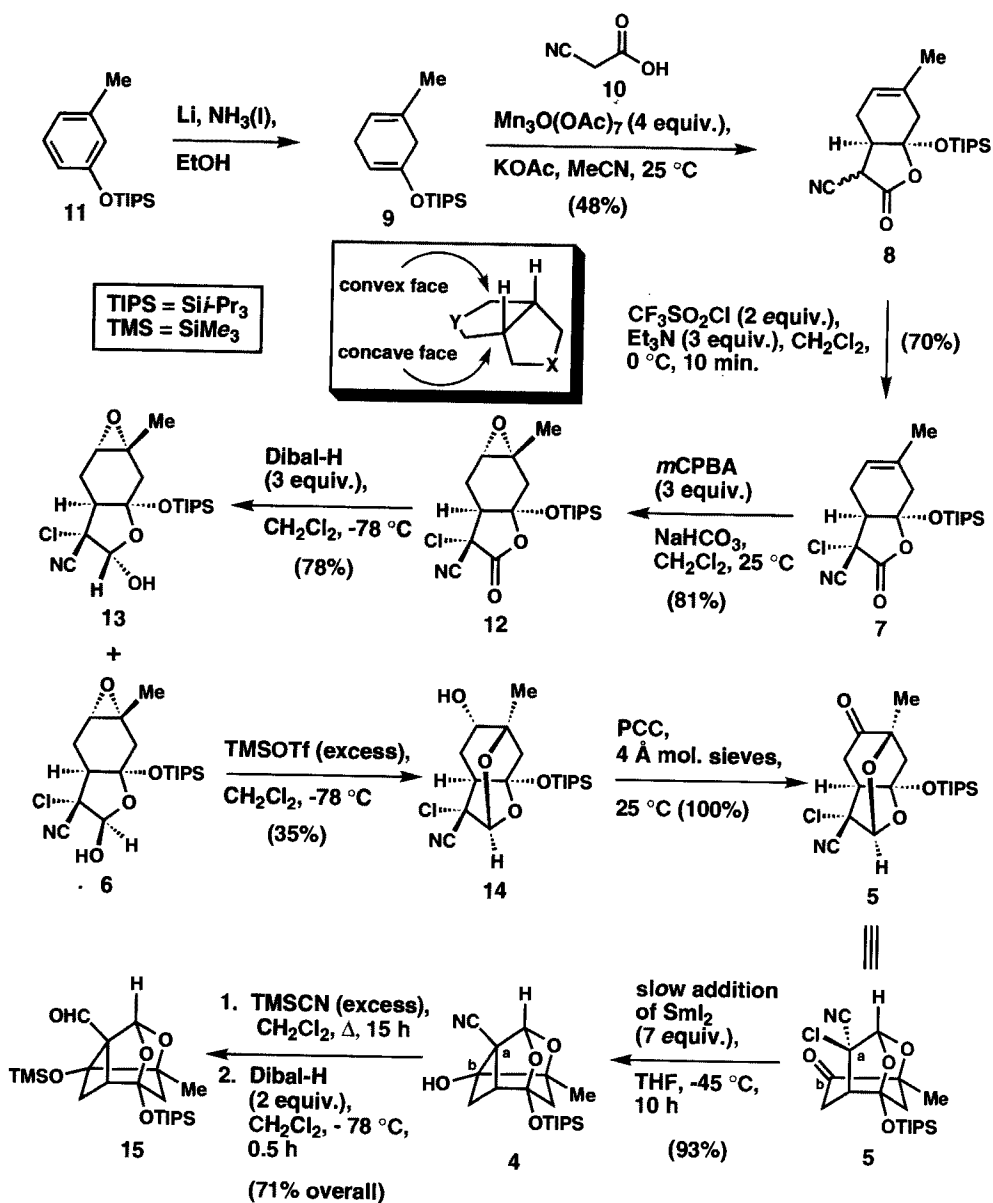


Scheme 1. Retrosynthetic analysis of paeoniflorin (1) and paeoniflorigenin (2).

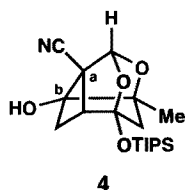
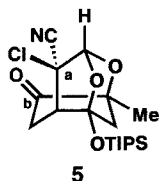
32.3 Total Synthesis



Corey's synthesis of paeoniflorigenin (**2**) commences with a Birch reduction⁶ of the triisopropylsilyl ether of *meta*-cresol (**11**) to give intermediate **9**, the substrate for the crucial carbolactonization reaction (see Scheme 2). It is interesting to note that intermediate **9** already contains seven out of a total of ten carbon atoms that constitute the pinane carbon frameworks of **2** and **1**, and it provides a suitable platform upon which the remaining three carbon atoms can be introduced. On the basis of some encouraging precedents established previously by the Corey group,⁷ it was projected that intermediate **9** could serve as a substrate for a Mn^{III} -promoted carbolactonization reaction with cyanoacetic acid (**10**). In the event, treatment of a solution of dihydro-*meta*-cresol triisopropylsilyl ether (**9**) in acetonitrile with four equivalents of $\text{Mn}_3\text{O}(\text{OAc})_7$ and twenty equivalents of cyanoacetic acid (**10**) at room temperature produces α -cyano- γ -lactone **8** in a yield of 48%. Aromatization of **9** to **11** is the major side reaction in this step. Intermediate **8** is an interesting bicyclic molecule which can be manipulated in a stereocontrolled fashion by virtue of its folded molecular framework. For example, removal of the active methine hydrogen adjacent to the electron-withdrawing cyano and lactone carbonyl groups in **8** with base would afford a resonance-stabilized enolate which possesses two diastereotopic faces. It is instructive to note that one enolate diastereoface, the concave face, is considerably more hindered than the convex face⁸ (see insert in Scheme 2). It is thus possible to achieve a completely diastereoselective α -chlorination of the enolate derived from **8** with trifluoromethanesulfonyl chloride to give intermediate **7** in 70% yield. The source of electrophilic chlorine engages the more accessible convex face of the enolate. The folded framework of intermediate **7** also permits a completely diastereoselective oxidation of the trisubstituted olefin. In the presence of *m*CPBA, the more accessible convex olefin diastereoface in **7** is oxidized to give epoxide **12** in diastereomerically pure form. A chemoselective partial reduction of the lactone carbonyl in **12** with diisobutylaluminum hydride (Dibal-H) provides a mixture of epimeric lactols **13** and **6** in a combined yield of 78%. Not surprisingly, both of these substances are rather unstable and decompose readily in the presence of base or silica gel to give an unstable keto aldehyde. The unstable, stereoisomeric lactols **13** and **6** were, therefore, neither separated nor interconverted. Interestingly, the action of trimethylsilyl triflate on the mixture induces the selective conversion of lactol **6** to hydroxy tricyclic ether **14**. Trimethylsilyl triflate provides suitable activation of the oxirane ring in **6** and induces a transannular etherification reaction to give **14**. Oxidation of the secondary hydroxyl group in **14** with pyridinium chlorochromate (PCC) results in the formation of ketochloronitrile **5** in quantitative yield.



Scheme 2. Synthesis of intermediate 15.

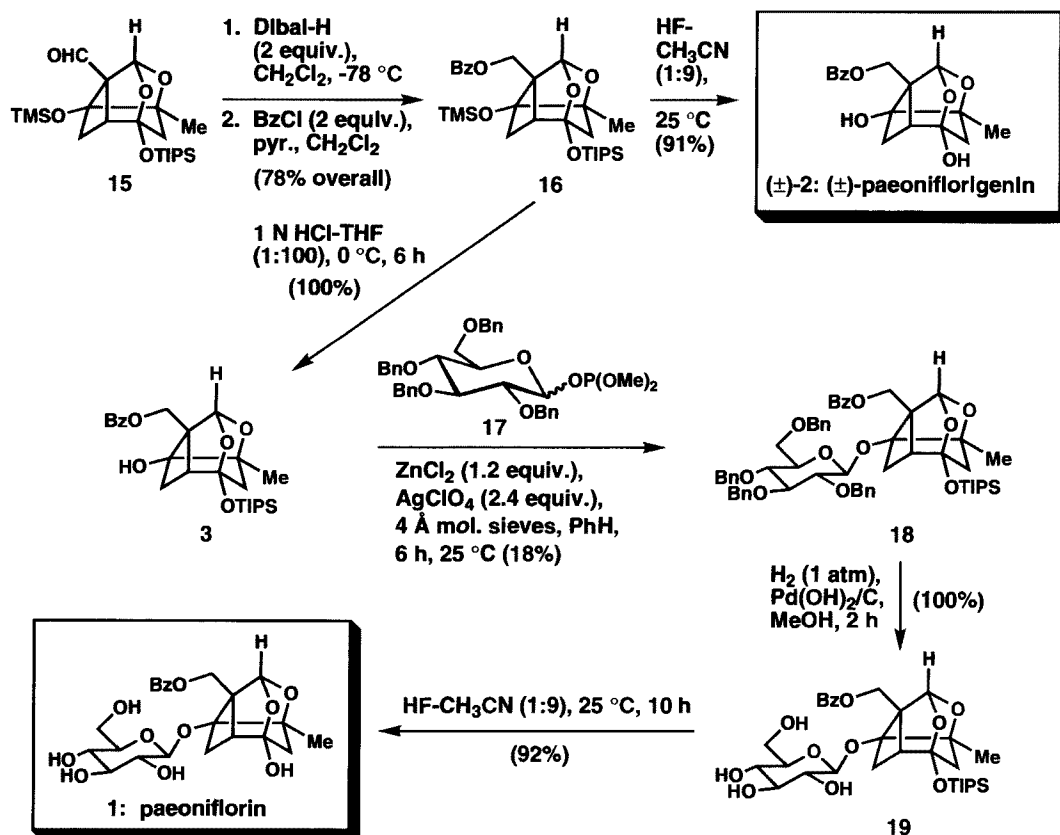


Within the compact structure of intermediate **5**, the ketone carbonyl and the chlorine-bearing carbon atom occupy proximal regions of space, and the prospects for achieving the formation of a bond between carbons *a* and *b* through some reductive process seem excellent. When a cold (-45°C) solution of ketochloronitrile **5** in THF is treated with samarium diiodide, the carbon–chlorine bond is reduced and a new bond is formed between carbons *a* and *b* to give intermediate **4** in an excellent yield of 93%! In retrospect, this particular strategy for creating the key *a*–*b* bond seems rather daring because α -oxygenated ketones are known to be susceptible to reduction in the presence of samarium diiodide.⁹ In fact, a wide range of α -heterosubstituted ketones can be reduced under mild conditions with samarium diiodide to give unsubstituted ketones.⁵

The mechanism for the transformation of **5** to **4** was not addressed. However, it seems plausible that samarium diiodide accomplishes a reduction of the carbon–chlorine bond to give a transient, resonance-stabilized carbon radical which then adds to a Sm^{III} -activated ketone carbonyl or combines with a ketyl radical. Although some intramolecular samarium(II)-promoted Barbier reactions do appear to proceed through the intermediacy of an organo-samarium intermediate (i.e. a Sm^{III} carbanion),¹⁰ it is probable that a β -elimination pathway would lead to a rapid destruction of intermediate **5** if such a species were formed in this reaction. Nevertheless, the facile transformation of intermediate **5** to **4**, attended by the formation of the strained four-membered ring of paeoniflorigenin, constitutes a very elegant example of an intramolecular samarium-mediated Barbier reaction.

β -Hydroxynitrile **4** is a rather unstable substance and undergoes a rapid retro aldol-type cleavage of the cyclobutane ring in the presence of even mild bases. Fortunately, however, it was found that the action of trimethylsilyl cyanide (without added base) on intermediate **4** could accomplish the protection of the bridgehead tertiary hydroxyl group to give, after reduction of the nitrile group with Dibal-H, aldehyde **15** in an overall yield of 71% from **4**. Further reduction of the aldehyde with Dibal-H, followed by benzoylation of the neopentyl primary hydroxyl with benzoyl chloride, provides intermediate **16** in 78% overall yield (see Scheme 3).

An important task still remaining to be completed for the synthesis of paeoniflorin is the selective glycosidation of the tertiary hydroxyl group which is protected in the form of a trimethylsilyl ether in intermediate **16**. Thus, it is significant that exposure of **16** to 1N HCl in THF at 0°C results in the completely selective and quantitative cleavage of the trimethylsilyl ether to give intermediate **3**, a suitably differentiated molecule for the projected glycosidation reaction. On the other hand, exposure of either **16** or **3** to 1:9 50% aqueous hydrofluoric acid/acetonitrile at 23°C brings about the removal of both silyl protecting groups to give (\pm)-paeoniflorigenin [(\pm)-**2**]. Synthetic (\pm)-paeoniflorigenin [(\pm)-**2**] was isolated as the bistrimethylsilyl derivative and was found to be identical to the bistrimethylsilyl ether of natural paeoniflorigenin (**2**).



Scheme 3. Synthesis of paeoniflorin (**1**) and (±)-paeoniflorigenin [(±)-**2**].

With its free tertiary hydroxyl group, intermediate **3** seems poised for the crucial glycosidation reaction and the completion of the synthesis of paeoniflorin (**1**). After a good deal of systematic study, it was found that the method of Watanabe et al.¹¹ could achieve the glycosidation of **3** with intermediate **17**, the 1-dimethylphosphite derivative of the tetrabenzyl ether of glucose, to give a 1:1 mixture of **18** and its α anomer, and the corresponding 1:1 mixture of α and β anomers from the enantiomer of **3** in a total yield of 71 %. After careful purification, intermediate **18** could be obtained in stereoisomerically pure form in 18 % yield. Despite the impressive array of methods that have been developed for the purpose of achieving stereocontrolled glycosidic bond constructions,¹² the inefficiency of the conversion of **3** to **18** reveals a deficiency that still exists in methodology for the β -glycosidation of tertiary and other hindered alcohols.

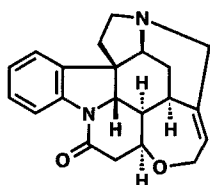
The completion of the synthesis of **1** only requires two deprotection steps. Hydrogenolysis of the four benzyl ethers, followed by cleavage of the triisopropylsilyl ether with hydrofluoric acid in acetonitrile, provides paeoniflorin (**1**) in an overall yield of 92 %.

32.4 Conclusion

Although paeoniflorin is not a large molecule, it is very complex. Corey's instructive synthesis of this natural product employs a number of novel and stereoselective transformations. Starting from a readily available aromatic compound, the strained, cagelike pinane framework of paeoniflorin is constructed by an eight-step reaction sequence that features regioselective carbolactonization and intramolecular samarium Barbier reactions. The former reaction produces a *cis*-fused bicyclic γ -lactone. The folded molecular framework of this substance is distinguished by a hindered concave face and a relatively unhindered convex face. This useful property was exploited by Corey for the purpose of achieving a completely diastereoselective oxidation reaction (see **7** \rightarrow **12**, Scheme 2). The SmI_2 -induced cyclization reaction is also noteworthy. This reductive cyclization reaction is remarkably efficient and constitutes an elegant example of a samarium Barbier reaction; it accomplishes the formation of a key carbon-carbon bond and completes the synthesis of the strained molecular skeleton of paeoniflorin.¹³

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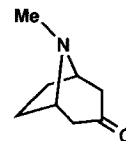
1: strychnine

L. E. Overman (1993)

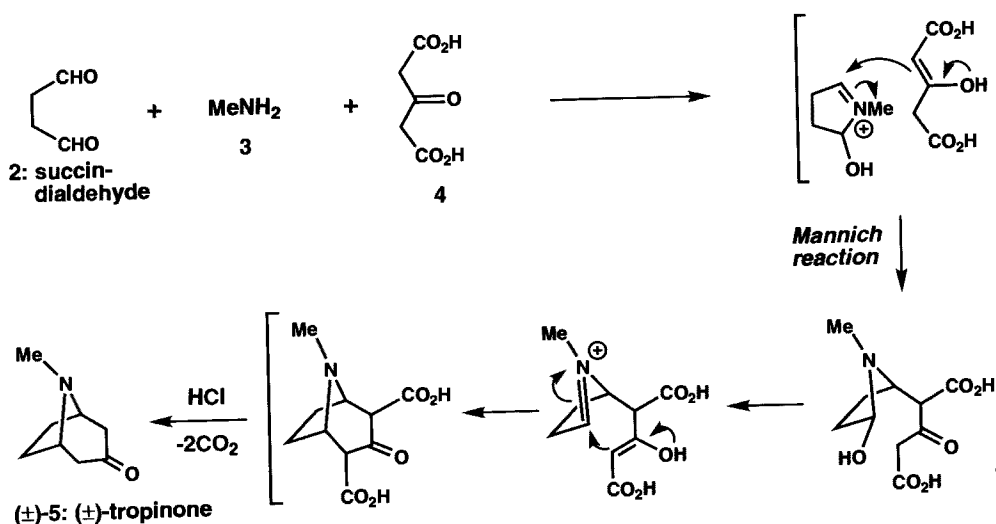
Strychnine

33.1 Introduction

A most impressive transformation in the biosynthesis of cholesterol is the enzyme-catalyzed conversion of the squalene oxide molecule into lanosterol and the related conversion of squalene oxide into the plant triterpenoid dammaradienol (see Scheme 1a in Chapter 6). In one dramatic step, a complex tetracyclic framework possessing no less than seven stereogenic centers is assembled from a flat polyolefin chain.¹ Although 128 stereoisomeric substances could conceivably be produced, only one is formed! In R. Robinson's elegant biomimetic synthesis of (\pm)-tropinone [(\pm)-**5**],² the combination of succindialdehyde (**2**), methylamine (**3**), and either acetone or a salt of acetone dicarboxylic acid (**4**) results in the formation of tropinone through consecutive inter- and intramolecular Mannich reactions (see Scheme 1). These impressive examples illustrate, in a particularly striking way, the marked increase in molecular complexity that can attend the employment of tandem (or sequential) transformations.³ A tandem transformation pertains to any sequence of reaction steps in which several bonds are formed or broken without the isolation of any intermediates.^{3a} In addition to their aesthetic appeal, tandem or sequential transformations can be highly atom economical.⁴ In an ideal situation, all of the atoms contained within a starting material are expressed in some form in the desired product. In this chapter, we present a beautiful application of a tandem cationic aza-Cope rearrangement/Mannich cyclization strategy to an enantioselective synthesis of (–)-strychnine (**1**) by L. E. Overman and his group at U.C. Irvine.⁵

(±)-**5**: (±)-tropinone

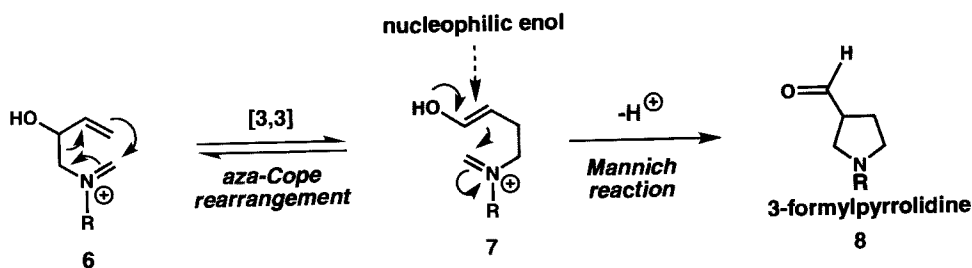
Overman's cationic aza-Cope/Mannich strategy is predicated on the observation that the presence of a charged atom in a molecular



Scheme 1. Robinson's synthesis of (±)-tropinone [(±)-5].

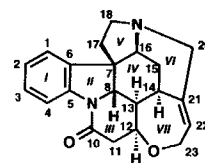
assembly undergoing bond reorganization can substantially reduce the free energy of activation for the process.⁶ As a result, reactions of charged species can be performed at lower temperatures, often with enhanced selectivity.⁷ The aza-Cope/Mannich reaction developed by the Overman group has performed admirably in a variety of contexts,⁸ and has been employed as the key operation in the synthesis of a number of structurally complex alkaloids.^{6a,9} The parent cationic aza-Cope/Mannich cyclization is illustrated in Scheme 2.

The aza-Cope/Mannich reaction takes advantage of the facility with which a γ,δ -unsaturated iminium ion, such as **6**, participates in a [3,3] sigmatropic rearrangement to give an isomeric species which is suitably functionalized for an intramolecular and irreversible Mannich cyclization (see intermediate **7**). The aza-Cope rearrangement substrate **6** is simply an unsaturated iminium ion which can be fashioned in a number of ways from a homoallylic



Scheme 2. The aza-Cope/Mannich reaction.

amine containing a hydroxyl group in the 2-position. It is noteworthy that the cationic aza-Cope rearrangement/Mannich cyclization process can be induced under extremely mild conditions (i.e. neutral pH and ambient temperature). Once intermediate **7** is produced, it can obviously revert back to **6** through a Cope rearrangement or it can participate in an irreversible and highly exothermic Mannich cyclization to give 3-formylpyrrolidine (**8**). Thus, by stressing the equilibrium between intermediates **6** and **7** in this way, it is possible to bring about a smooth conversion of a simple unsaturated iminium ion to a 3-acylpyrrolidine, a common substructure of a diverse collection of alkaloids. The asymmetric total synthesis of (–)-strychnine (**1**) by the Overman group provides a powerful illustration of the utility of the tandem aza-Cope/Mannich reaction as a tool for the construction of complex alkaloids.



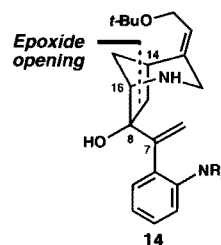
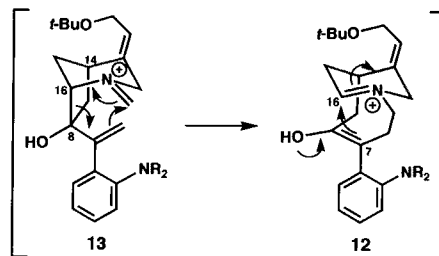
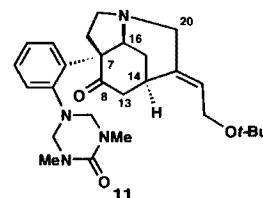
1: strychnine

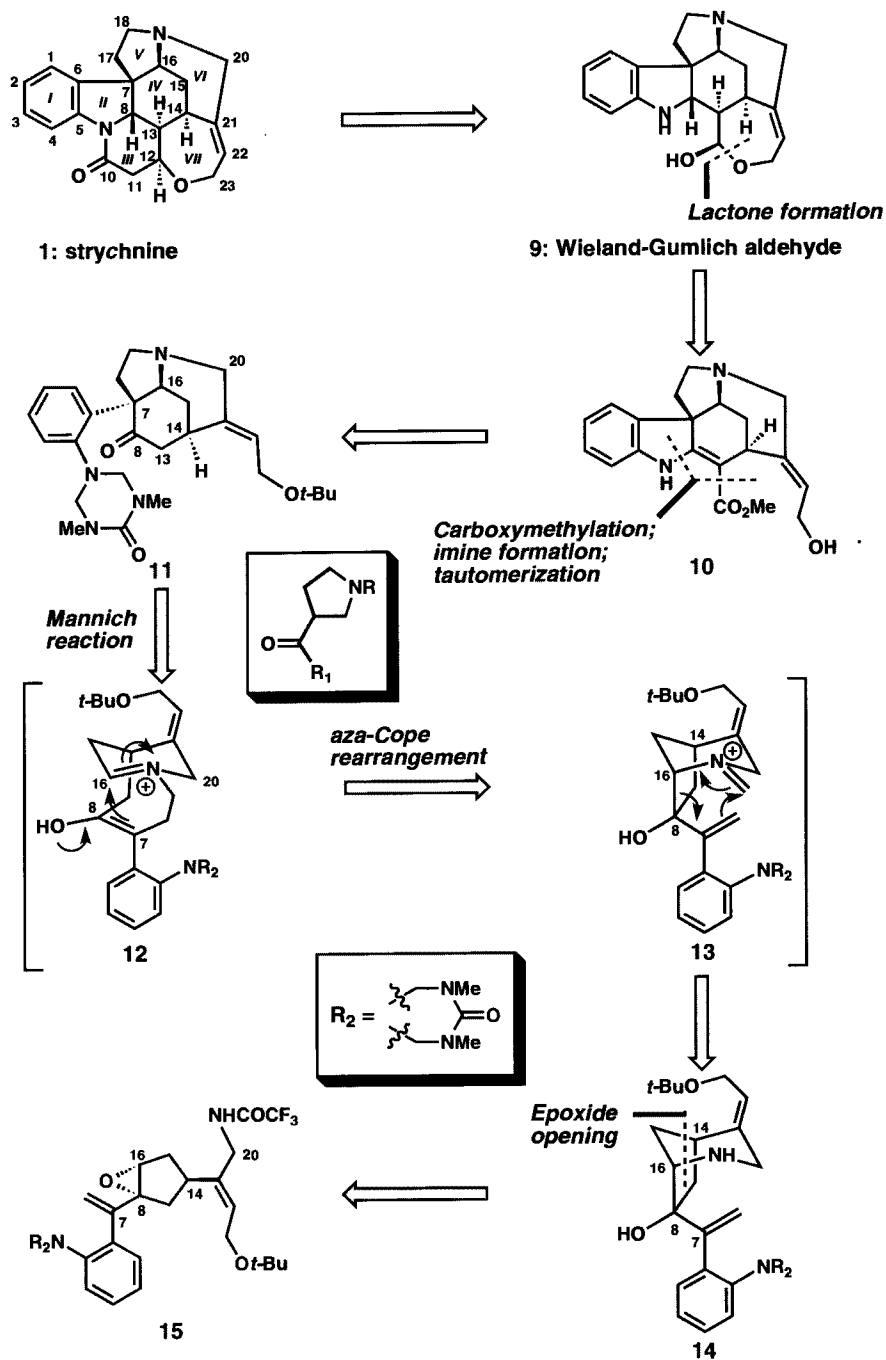
33.2 Retrosynthetic Analysis and Strategy

The general features of this impressive synthesis are outlined retrosynthetically in Scheme 3. Retrosynthetic disassembly of ring III of strychnine (**1**) leads back to Wieland-Gumlich aldehyde **9**, a key intermediate which had already been converted to strychnine in a single step by Anet and Robinson in 1953.¹⁰ Intermediate **10**, derived retrosynthetically from intermediate **9**, can be traced to ketone **11** by cleavage of the indicated bonds. In the synthetic direction, carboxylation of C-13 in intermediate **11** with methyl cyanoformate, followed by removal of the 1,3-dimethylhexahydro-2-oxo-1,3,5-triazine (triazone) protecting group from the aniline nitrogen atom, could conceivably produce intermediate **10** after intramolecular condensation with attendant dehydration.

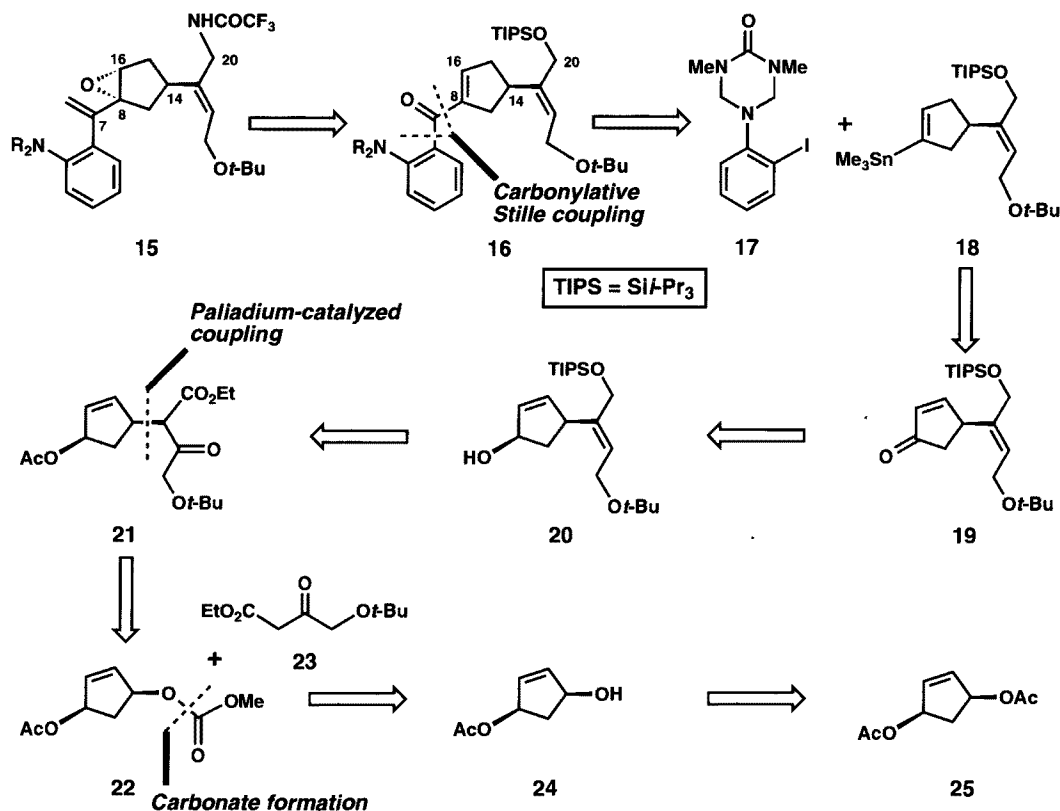
With three stereocenters, one of which is quaternary,¹¹ intermediate **11** is still rather imposing. However, as complex as **11** may appear, its 3-acylpyrrolidine substructure (see insert, Scheme 3) satisfies the structural prerequisite for the elegant and productive tandem aza-Cope/Mannich transform.¹² It is conceivable that intermediate **11** could be elaborated from azabicyclo[3.2.1]octanol **14** in one impressive step. On the basis of relevant precedent,⁹ it was anticipated that exposure of **14** to paraformaldehyde and a dehydrating agent would furnish iminium ion **13**. The intermediacy of **13** is expected to be brief, for it should undergo a facile cationic aza-Cope rearrangement to give the isomeric iminium ion **12** (see arrows). With a nucleophilic enol and an electrophilic iminium ion in spatial proximity, **12** should obligingly participate in a highly exothermic Mannich cyclization to give intermediate **11** (see arrows).

The *trans* relationship between the ring nitrogen appended to C-16 (strychnine numbering) and the C-8 tertiary hydroxyl group in **14** could conceivably be secured through an intramolecular S_N2





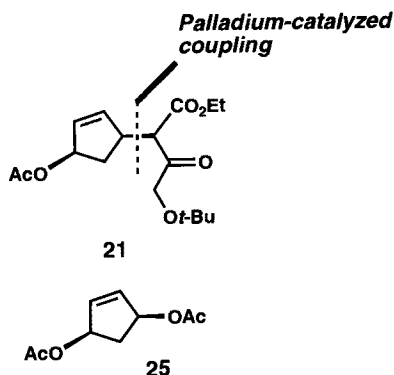
Scheme 3. Retrosynthetic analysis of strychnine (1).



Scheme 3. Retrosynthetic analysis of strychnine (**1**) (continued).

opening of a C8-C16 epoxide by a suitably disposed nitrogen substituent. Intramolecular aminolysis of the oxirane ring in **15** (Scheme 3), followed by cleavage of the *N*-trifluoroacetyl grouping, would appear to constitute a very straightforward approach to the synthesis of the key azabicyclo[3.2.1]octanol **14**. Intermediate **16** (Scheme 3), the retrosynthetic precursor of **15**, is functionalized in a manner which should permit a diastereoselective epoxidation of the C8-C16 double bond. In particular, the attack of a nucleophilic oxidant, such as *tert*-butyl hydroperoxide, upon enone **16** should take place at the less hindered α face of the enone carbon-carbon double bond. Exposure of the resultant α,β -epoxy ketone to (methylene)triphenylphosphorane, followed by a few functional group transformations at C-20, could then give **15**. Enone **16** could itself be formed through a palladium-catalyzed carbonylative cross-coupling¹³ of the triazone-protected *ortho*-iodoaniline **17** with vinylstannane **18** (Scheme 3).

Through a straightforward sequence of functional group manipulations, intermediate **18** could ultimately be derived from intermediate **21**. Retrosynthetic cleavage of the indicated carbon-carbon



bond in **21** provides intermediates **22** and **23** as potential precursors. In the synthetic direction, a chemo- and stereoselective palladium-catalyzed displacement of the allylic carbonate group¹⁴ in **22** with sodium ethyl *α*-*tert*-butoxyacetoacetate could furnish intermediate **21**. The use of enzymes to accomplish the asymmetrization of *meso* diols or their derivatives constitutes an important and practical development in organic synthesis.¹⁵ Through the agency of an enzyme and on the basis of sound precedent,¹⁶ it is entirely possible that prochiral *meso* 1,4-diacetoxycyclopent-2-ene (**25**) could be converted to intermediate **24** with high stereoselectivity. A trivial functional group transformation would then complete the preparation of **22** in enantiomerically enriched form.

33.3 Total Synthesis

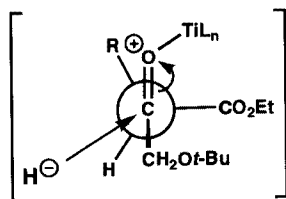
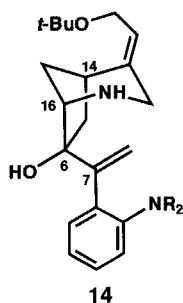
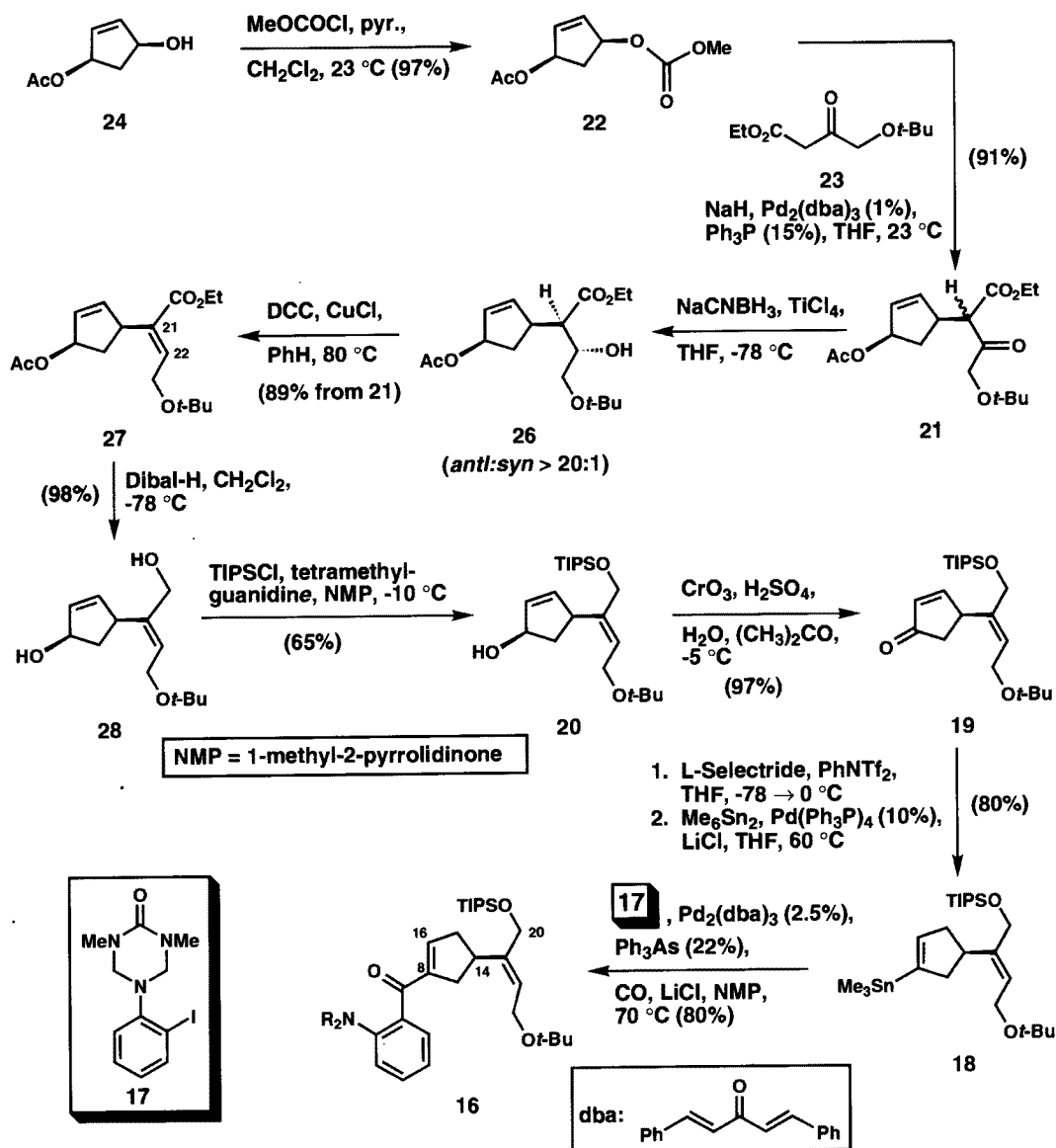
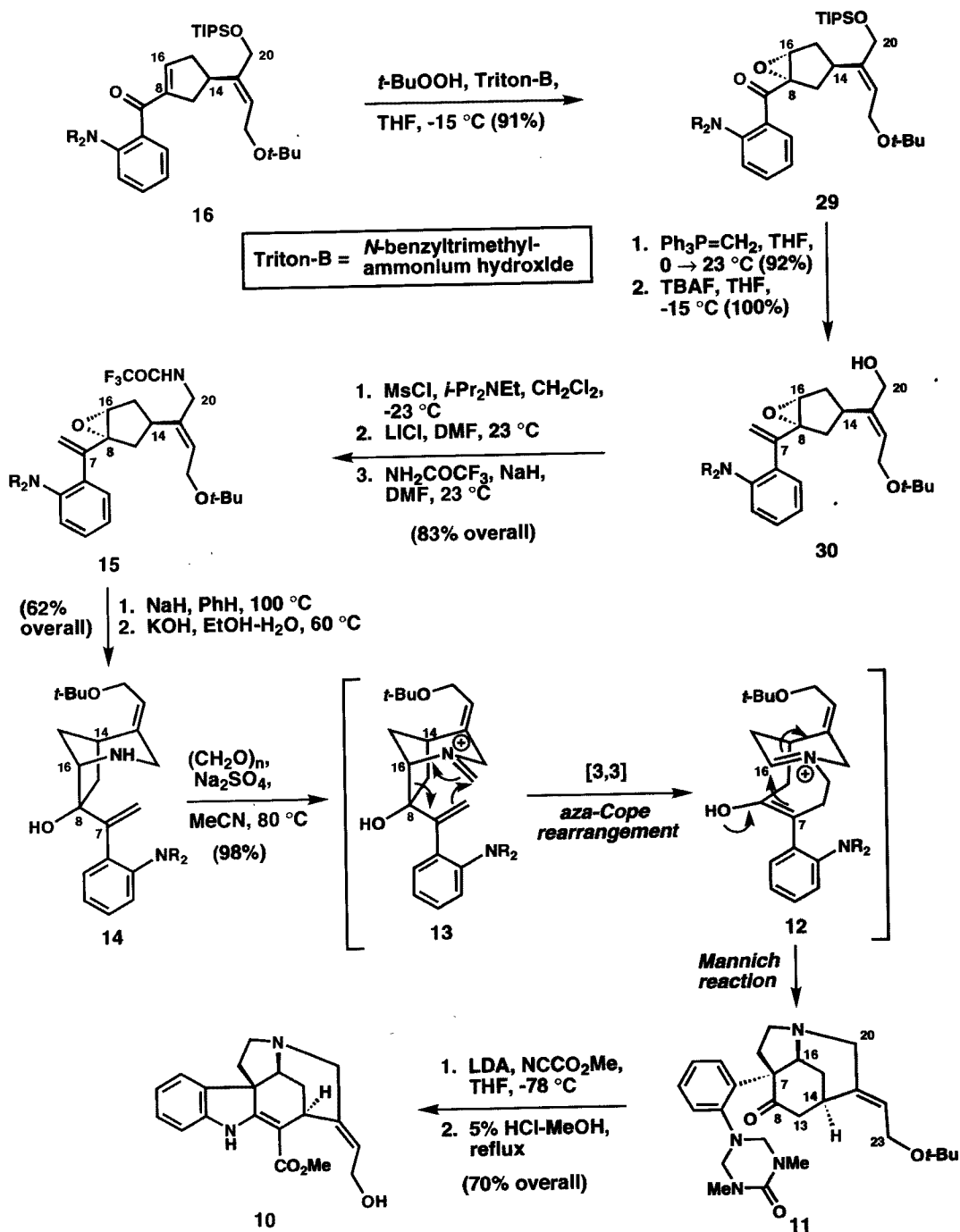


Figure 1. Presumed transition state for reduction of β -keto ester **21**. Only one C-21 epimer is shown for clarity.

The first objective is the enantioselective synthesis of unsaturated azabicyclo[3.2.1]octanol **14**, the key aza-Cope/Mannich rearrangement substrate (see Schemes 4 and 5). Reaction of methyl chloroformate with (1*R*,4*S*)-(+)-4-hydroxy-cyclopent-2-en-4-yl acetate (**24**), a substance readily available in high enantiomeric purity from the action of electric eel acetylcholinesterase on *cis*-1,4-diacetoxycyclopent-2-ene (**25**),¹⁶ provides intermediate **22** in 97% yield. On the basis of relevant precedent,¹⁴ it was anticipated that the allylic carbonate in **22** could be displaced in a completely chemo- and stereoselective manner with a carbon nucleophile. Indeed, treatment of a solution of **22** in THF with sodium ethyl *α*-*tert*-butoxyacetoacetate, 1% Pd₂(dba)₃, and 15% triphenylphosphine provides, through the intermediacy of a π -allyl palladium species, *cis* adduct **21** as a 1:1 mixture of diastereoisomers in 91% yield. Reduction of the 1:1 mixture of β -keto esters with excess sodium cyanoborohydride in the presence of 1.1 equivalents of titanium(IV) chloride affords, with high stereoselectivity (>20:1), the corresponding *anti* β -hydroxy esters **26** in nearly quantitative yield. The observed stereochemical course of the reduction of **21** is consistent with a Felkin-Anh model (see Figure 1).¹⁷ The action of 1,3-dicyclohexylcarbodiimide (DCC) and cuprous chloride on the mixture of *anti* β -hydroxy esters induces a smooth *syn* dehydration¹⁸ to give, after chromatographic purification, (*E*)-butenoate **27** in an overall yield of 89% from **21**. It is noteworthy that this simple sequence of reactions permits the construction of the requisite *trans* C21-C22 double bond (strychnine numbering). Treatment of **27** with excess diisobutylaluminum hydride (Dibal-H) accomplishes the reduction of the ethyl ester to the corresponding alcohol and the removal of the acetyl group to give diol **28** in an excellent yield of 98%. Selective silylation of the primary allylic hydroxyl group with triisopropylsilyl chloride and 1,1,3,3-tetramethylguanidine at -10°C in 1-methyl-2-pyrrolidinone (NMP) provides intermediate **20**, which is subse-



Scheme 4. Synthesis of intermediate 16.



Scheme 5. Synthesis of intermediate **10**.

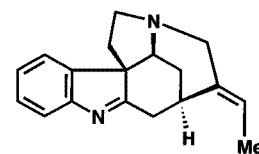
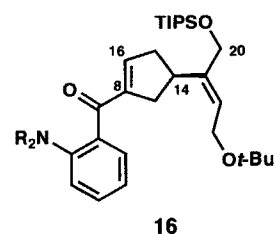
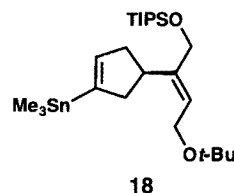
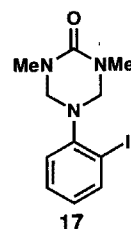
quently oxidized with Jones reagent to give enone **19** in an overall yield of 63 %.

A key transformation in the elaboration of azabicyclo[3.2.1]octanol **14** is a palladium-catalyzed carbonylative cross-coupling¹³ of intermediates **17** and **18** to give **16** (see Scheme 3). Intermediate **17** is available from *ortho*-iodoaniline,¹⁹ and vinylstannane **18** is obtained in an overall yield of 80 % through conjugate reduction of enone **19** with L-Selectride, triflation of the enolate oxygen with *N*-phenyltriflimide,²⁰ and palladium-catalyzed coupling of the resultant enol triflate with hexamethylditin²¹ (see Scheme 4). Using conditions that were optimized for a related transformation,⁹ it was found that aryl iodide **17** and vinylstannane **18** can be joined convergently through a carbonyl bridge to give enone **16** in a yield of 80 %.

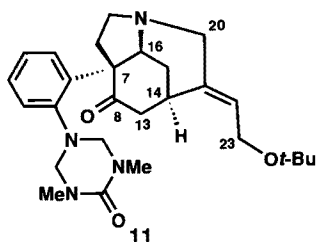
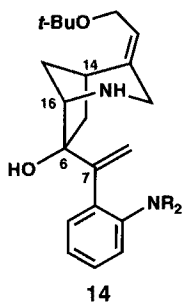
A second crucial transformation in the synthesis of azabicyclo[3.2.1]octanol **14** is the intramolecular aminolysis of the oxirane ring in intermediate **15** (see Scheme 3). It was anticipated at the outset that the appendage attached to C-14 (strychnine numbering) in **16** should block access to the β face of the enone carbon-carbon double bond. In the company of a suitable oxidant, it ought to be possible to bring about a diastereoselective epoxidation of the much less hindered α face of the $\Delta^{8,16}$ double bond. Indeed, when enone **16** is subjected to the action of basic *tert*-butyl hydroperoxide at -15°C in THF, the $\Delta^{8,16}$ enone double bond is oxidized in a chemo- and stereoselective fashion to give α,β -epoxy ketone **29** in 91 % yield (see Scheme 5). Wittig methylenation of the ketone carbonyl in **29**, followed sequentially by fluoride-induced cleavage of the C-20 triisopropylsilyl ether, $\text{S}_{\text{N}}2$ displacement of the derived allylic mesylate with chloride ion, and $\text{S}_{\text{N}}2$ displacement of the resultant allylic chloride with sodium trifluoroacetamide, results in the synthesis of intermediate **15** in excellent overall yield.

The hydrogen atom bound to the amide nitrogen in **15** is rather acidic and it can be easily removed as a proton in the presence of some competent base. Naturally, such an event would afford a delocalized anion, a nucleophilic species, which could attack the proximal epoxide at position 16 in an intramolecular fashion to give the desired azabicyclo[3.2.1]octanol framework. In the event, when a solution of **15** in benzene is treated with sodium hydride at 100°C , the processes just outlined do in fact take place and intermediate **14** is obtained after hydrolytic cleavage of the trifluoroacetyl group with potassium hydroxide. The formation of azabicyclo[3.2.1]octanol **14** in an overall yield of 43 % from enone **16** underscores the efficiency of Overman's route to this heavily functionalized bicycle.

The prerequisite for an evaluation of the utility of the aza-Cope/Mannich strategy for a synthesis of strychnine has now been satisfied. Using unsaturated azabicyclo[3.2.1]octanols closely related to **14**, the Overman group had previously demonstrated the impressive facility with which the aza-Cope/Mannich reaction can construct the complex molecular frameworks of (\pm)-dehydrotubifoline and

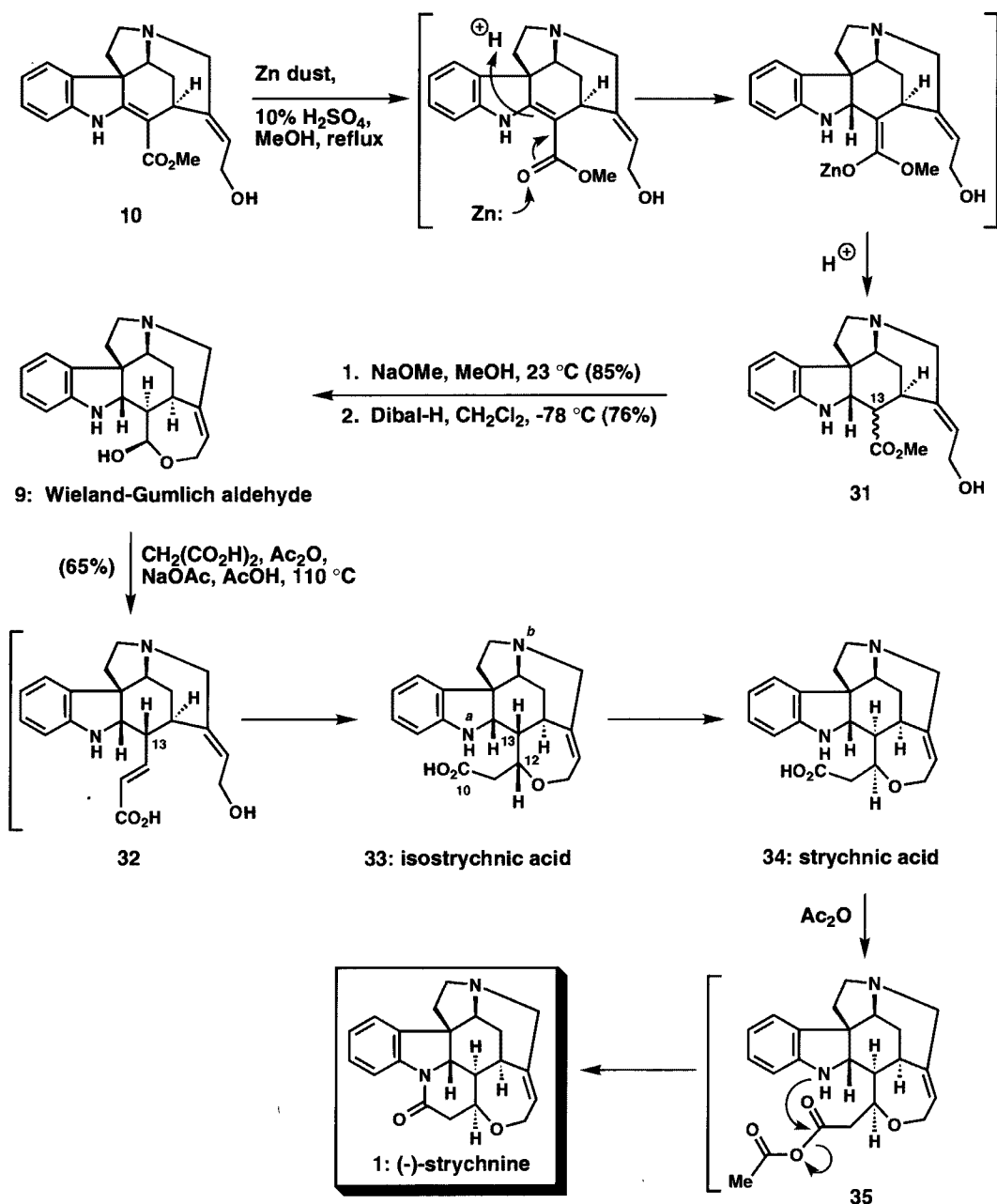


(\pm)-dehydrotubifoline



(\pm)-akuammicine.⁹ These two examples provide striking testimony to the value of Overman's tandem aza-Cope/Mannich reaction for the construction of complex *Strychnos* alkaloids. The combination of intermediate **14**, excess paraformaldehyde, and anhydrous sodium sulfate in hot acetonitrile leads, through the intermediacy of isomeric iminium ions **13** and **12** (Scheme 5), to the formation of crystalline **11** in 98% yield! Interestingly, this reaction was performed on an 800 mg scale without any added acid. Presumably, trace amounts of formic acid in the paraformaldehyde are sufficient to catalyze the formation of the iminium ion.⁹

From intermediate **11**, the path to strychnine is a straightforward one. Carboxylation of the lithium enolate derived from ketone **11** with methyl cyanoformate,²² followed by exposure of the resultant β -keto ester to 5% HCl in refluxing methanol, results in the formation of vinylogous carbamate **10** (see Scheme 5) in an overall yield of 70%. Under these acidic conditions, the *tert*-butyl ether attached to C-23 is hydrolyzed, and the aniline nitrogen is freed from its triazone protecting group. The unveiled primary amino group can then attack the proximal electrophilic carbon at position 8 in an intramolecular fashion to give intermediate **10** after expulsion of a molecule of water. Saturation of the vinylogous carbamate in **10** with zinc dust in acidic methanol²³ provides intermediate **31** as a mixture of C-13 epimers, presumably through the processes illustrated in Scheme 6. Exposure of intermediate **31** to sodium methoxide in methanol at 23°C induces epimerization at C-13 to give the known β ester which is subsequently reduced with diisobutylaluminum hydride to give Wieland-Gumlich aldehyde (**9**)²⁴ in a yield of 65% for the two steps. It had been demonstrated that this substance could, when subjected to the action of malonic acid, acetic acid, and acetic anhydride at 110°C, be converted directly to strychnine.¹⁰ It was also known from some important work by Robinson and Saxton²⁵ that treatment of the Wieland-Gumlich aldehyde (**9**) with malonic acid, pyridine, and piperidine results in the formation of isostrychnic acid (**33**), a substance with inverted configurations at C-12 and at C-13. This transformation probably proceeds through the intermediacy of **32** and it has been suggested that the inverted configuration at C-13 represents a thermodynamically more stable situation.²⁶ Although the configuration at C-13 in isostrychnic acid (**33**) prevents an intramolecular acylation of N^a with the C-10 carboxyl group (or an activated derivative), isostrychnic acid can, under the conditions illustrated in Scheme 6 and via intermediate **32**, undergo isomerization to strychnic acid (**34**). The action of acetic anhydride on strychnic acid then leads to the formation of (–)-strychnine (**1**) through the intermediacy of mixed-anhydride **35**. Overman's elegant synthesis of strychnine is now complete.



Scheme 6. Synthesis of (-)-strychnine (1).

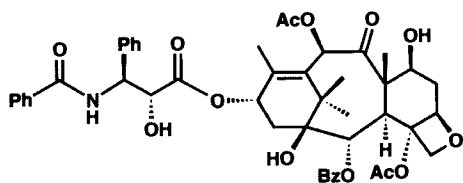
33.4 Conclusion

A hallmark of tandem or sequential reaction strategies is the impressive enhancement in molecular complexity that can result when such strategies are employed.³ In this spectacular synthesis of strychnine, advantage was taken of the facility with which a charged molecular framework can undergo bond reorganization. Through the combination of cationic aza-Cope and intramolecular Mannich reactions, a formidable molecule (intermediate **11**) was synthesized in short order and under extremely mild conditions. Overman's tandem cationic aza-Cope rearrangement/Mannich cyclization strategy is a sophisticated and powerful tool ideally suited for the construction of structurally complex, multifunctional alkaloids. This synthesis also demonstrates a variety of new reagents and reactions and the long way organic synthesis has come since the days of the Woodward synthesis²⁷ of strychnine (Chapter 2). The latter, of course, is to be admired for the sheer fact that it was done at that time and with the rather limited armamentarium then available to synthetic chemists.

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1: taxol

K. C. Nicolaou (1994)

Taxol

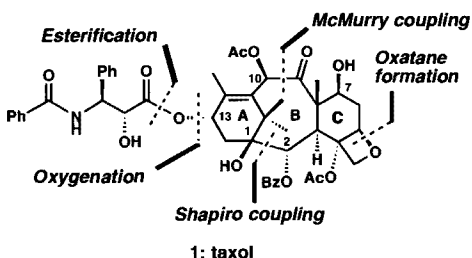
34.1 Introduction

The story of taxol (**1**), a molecule that received much publicity in the early 1990s, goes back to ancient times. Julius Caesar mentions in his “Gallic Wars” that Catuvolcus, a chieftain of the Eburones, committed suicide by taking extracts from the yew tree.¹ Several other accounts report more recent uses of such extracts as poison or as a cancer-healing folk medicine. The modern history of this natural product began in 1962, when A. Barclay collected bark from *Taxus brevifolia*, the Pacific Yew tree, from forests in the north-western United States, as part of a joint project between the U.S. Department of Agriculture and the National Cancer Institute aimed at the discovery of new anticancer agents.² An intense search for the cytotoxic principle led to the isolation of taxol in minute quantities. It has been estimated that the sacrifice of one 100-year-old yew tree would result in approximately only 300 mg of taxol, just about enough for one single dose for a cancer patient. In a seminal paper published in 1971,³ Wall, Wani, and coworkers reported the molecular structure of taxol on the basis of an X-ray crystallographic analysis.

Taxol's journey to the clinic was slow and arduous. Initial difficulties with aqueous solubility and lack of knowledge regarding its mechanism of action delayed its development until 1979 when, in another seminal paper in the field, S. B. Horwitz and her collaborators disclosed their findings on the interaction of taxol with microtubules.⁴ Taxol's unique biological action, which includes promotion of microtubule formation and microtubule stabilization, stimulated a renewed interest in taxol as a potential drug candidate. The problem of procuring adequate supplies of taxol became even

more acute when environmentalists, concerned about the endangered spotted owl that lives in the northwestern United States, raised objections to the destruction of the ancient forests. A potential solution was found when 10-deacetylbaccatin III, a precursor of taxol lacking the C-10 acetoxy group and the C-13 side chain, was discovered in the needles and twigs of *Taxus baccata*, the European Yew tree. Harvesting this renewable source, followed by semisynthesis,⁵ allows the production of taxol on a relatively large scale. In the meantime, synthetic chemists around the world embarked on different schemes to synthesize taxol. In 1992, taxol was approved for the treatment of ovarian cancer by the U.S. Food and Drug Administration, and it held promise for the treatment of several other types of cancer including breast, lung, and melanoma. By the fall of 1995, three distinct total syntheses of taxol had been disclosed.^{6,7,8} In this chapter, we discuss the synthesis developed in the Nicolaou laboratories, which was reported first in the journal *Nature*.

34.2 Retrosynthetic Analysis and Strategy



Although taxol's unique mode of action and potential as an anti-cancer agent underlie much of the intense interest in this celebrated diterpene, synthetic chemists were most impressed with taxol's structure. The taxol molecule (**1**) is distinguished by a 6-8-6 tricyclic carbon framework, by a characteristic ester side chain, and by a dense pattern of oxygenated functionality. Inspection of **1** reveals that of the fourteen carbon atoms defining the boundary of the molecule, nine are asymmetric and seven of these bear some form of oxygenation. Taxol's saturated six-membered C-ring is the site of an unusually heavy concentration of asymmetry; this imposing substructure contains five contiguous stereogenic centers, and it supports the unusual and potentially electrophilic oxetane ring.

Interestingly, the stereochemical challenge that would beset any synthetic approach is matched, and perhaps eclipsed, by the potentially serious problem presented by the central eight-membered carbocycle. On the basis of unfavorable entropy, bond angle deformations, and destabilizing transannular interactions, the eight-membered ring has traditionally been regarded as one of the most difficult to construct,^{9a} and the development of general methods for its synthesis has received a great deal of attention.^{9b} The powerful combination of the eight-membered ring and the array of oxygenated functionality decorating the periphery of the molecule make taxol an extremely challenging target for synthesis.

Not surprisingly, taxol has motivated the development of many synthetic strategies, and much fascinating science has emerged from research in this area.^{2,10} Attracted by the formidable challenge

posed by the structural complexity of taxol (**1**) and by the need for a synthetic entry into the taxoid class of compounds, the Nicolaou group embarked, in early 1992, on a total synthesis of this molecule.

Scheme 1 shows the structure of taxol (**1**) and the strategic bonds identified for retrosynthetic disconnection. Taking advantage of precedent in the field regarding the attachment of the ester side chain to the taxoid framework, the ester bond is first disconnected to provide, after suitable protections, the baccatin III derivative **2** and the β -lactam derivative **3** as potential precursors. The union of compounds **2** and **3**, followed by elaboration to the target molecule is a matter of following published protocols. To further simplify the taxoid skeleton, the C-13 oxygen is excised retrosynthetically from structure **2**, giving compound **4** as the precursor. At this point, serious consideration was given to the selection of a cyclic carbonate to protect the C1–C2 diol system. In addition to its role as a protecting group, the carbonate ring could conceivably provide the preorganization necessary to facilitate a projected ring closure to form taxol's eight-membered ring (see below). Moreover, it was anticipated that a cyclic carbonate could serve as a potential precursor to the desired C1-hydroxy, C2-benzoate system of taxol (see Figure 1). Thus, compound **5** presented itself as a key intermediate in the synthesis. In the synthetic direction, it was our hope that phenyllithium would react chemoselectively with the carbonate carbonyl in **5** to give **4** upon collapse of the tetrahedral intermediate (see Figure 1). As attractive as this transformation seemed, we were not unaware of the presence of several other electrophilic functional groups in addition to the carbonate carbonyl in **5**. Indeed, the carbon framework of **5** supports a variety of electrophilic groups and each could, in principle, react with a strong nucleophile such as phenyllithium. Nevertheless, this simple transformation was found to be feasible during the course of our taxol degradation/reconstitution studies.¹¹

Proceeding with the retrosynthetic analysis, it is now timely to address the issue of the rather sensitive oxetane ring. Disconnection of the C5–O bond as indicated in structure **5** and engagement of

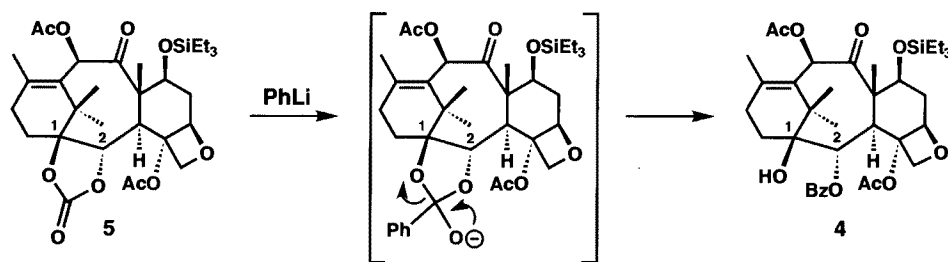
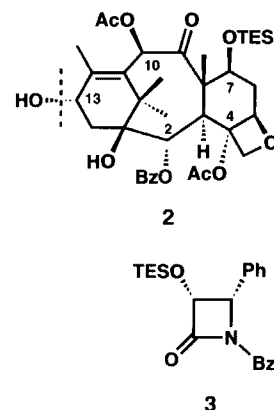
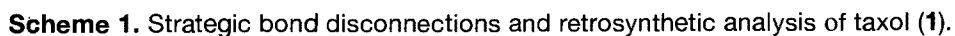


Figure 1. The cyclic carbonate \rightarrow hydroxybenzoate transformation.



the tertiary and primary hydroxyl groups extending from C-4 in a five-membered acetonide ring, reveals olefin **6** as a potential precursor. In the synthetic direction, introduction of an oxygen atom at C-5 to the desired face of the double bond in **6**, followed by an S_N2 -type displacement, or a direct ring closure of the primary hydroxyl on the double bond could accomplish the desired goal of forming the oxetane ring. The issue of constructing the C9–C10 functionality could conceivably be addressed from a C9–C10 diol system. As shown in Figure 2, the regio- and stereochemical outcome of manipulating the C9–C10 diol system to the desired C-9 keto, C-10 β -acetoxy system of taxol is left open, but with the possibility of correction via the indicated mechanism in the event that the wrong isomer is formed initially. Specifically, it was hoped that the presumed greater thermodynamic stability of the natural isomer would drive the equilibrium in the desired direction. With this expectation in mind, the eight-membered ring of compound **6** can be disassembled by a retro-pinacol coupling, providing dialdehyde **7** as a possible progenitor.

A conspicuous and valuable structural feature of **7** is the five-membered cyclic carbonate ring bridging the vicinal oxygen atoms attached to C-1 and C-2 (taxol numbering). An analysis of molecular models of compound **7** revealed that this cyclic protecting group might influence the projected pinacol coupling reaction in a favorable way by restricting rotational freedom. In fact, this analysis seemed to suggest that a cyclic protecting group bridging the C-1 and C-2 oxygen atoms would favor the adoption of a conformation

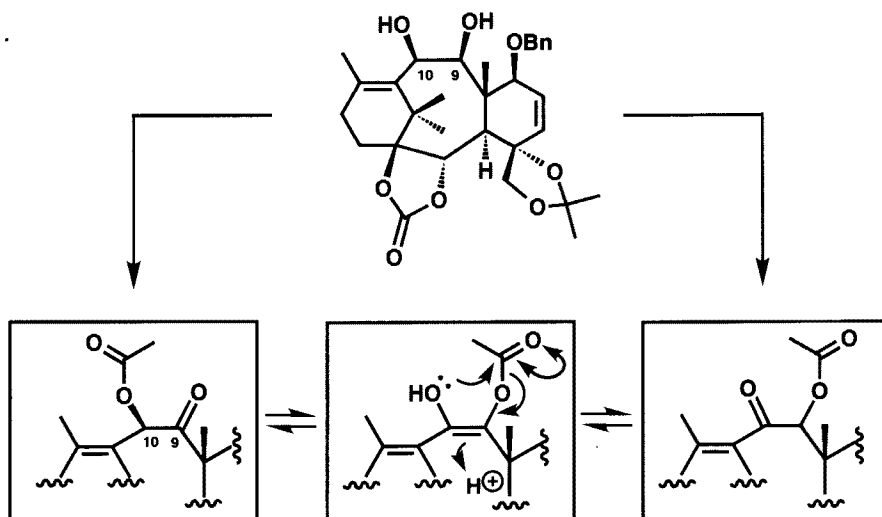
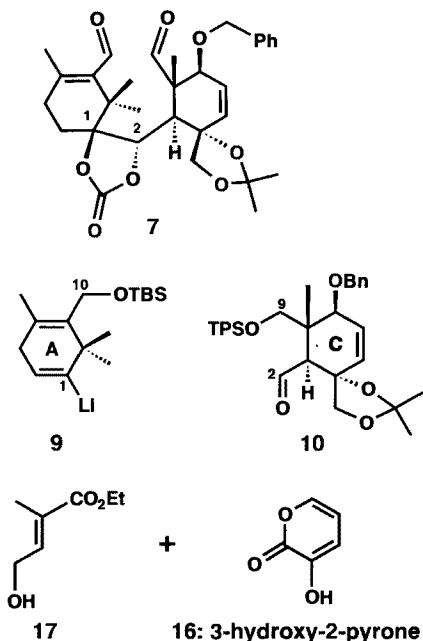


Figure 2. The C9–C10 regiochemistry problem.



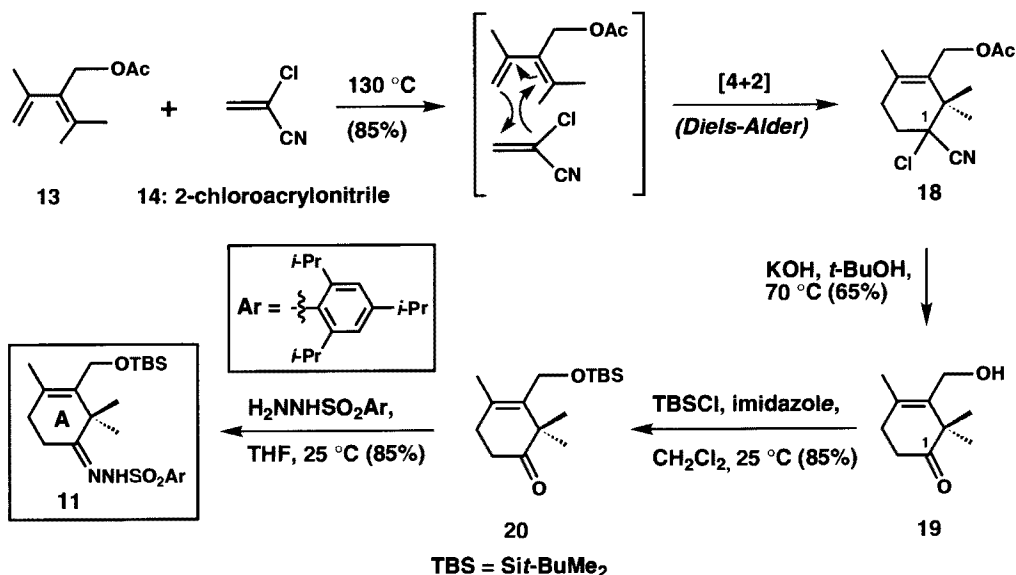
in which the two aldehyde functions are positioned in neighboring regions of space, which would clearly facilitate any process leading to their union. Although a host of cyclic protecting groups could conceivably provide the preorganization necessary to induce the crucial ring closure reaction, we were particularly interested in the cyclic carbonate because it can serve as a direct precursor to the C-1 hydroxy, C-2 benzoate system of the natural product (see Figure 1).

Removal of the carbonate ring from **7** (Scheme 1) and further functional group manipulations lead to allylic alcohol **8** which can be dissected, as shown, via a retro-Shapiro reaction to give vinyl-lithium **9** and aldehyde **10** as precursors. Vinyl lithium **9** can be derived from sulfonyl hydrazone **11**, which in turn can be traced back to unsaturated compounds **13** and **14** via a retro-Diels–Alder reaction. In keeping with the Diels–Alder theme, the cyclohexene aldehyde **10** can be traced to compounds **16** and **17** via sequential retrosynthetic manipulations which defined compounds **12** and **15** as possible key intermediates. In both Diels–Alder reactions, the regiochemical outcome is important, and special considerations had to be taken into account for the desired outcome to prevail. These and other regio- and stereochemical issues will be discussed in more detail in the following section.

34.3 Total Synthesis

The general strategy outlined in Scheme 1 is predicated on the convergent union of two prefabricated building blocks representing rings A and C, followed by the execution of an intramolecular bond-forming process to complete the tricyclic carbon framework of taxol. You will note that key intermediates **10** and **11** are simply functionalized cyclohexene rings. It, therefore, seemed prudent to devise a strategy for the construction of these two intermediates based on the powerful and predictable Diels–Alder reaction.¹²

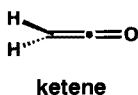
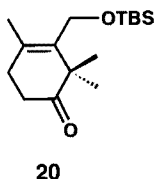
The synthesis of hydrazone **11** commences with an intermolecular Diels–Alder reaction between diene **13** and the commercially available ketene equivalent, 2-chloroacrylonitrile (**14**) (see Scheme 2).¹³ When these simple starting materials are confined to a sealed tube and heated at 130°C for three days, crystalline cyclohexene **18** is produced in 85% yield. Interestingly, and perhaps somewhat surprisingly, **18** is the only regioisomer formed in this reaction. On the basis of the substitution pattern of diene **13**, it was anticipated that **18** ought to be the major product formed in this process. However, considering that the Diels–Alder reaction is susceptible to steric effects, we were concerned that destabilizing nonbonding interactions in the transition state leading to the desired regioisomer **18** might prohibit, or at least hinder its formation. Nonetheless,



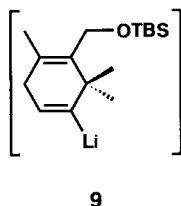
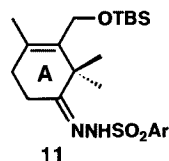
Scheme 2. Synthesis of hydrazone **11**.

compounds **13** and **14** combine smoothly under the indicated conditions to give, after silica gel chromatography, the desired adduct **18**. It was not possible to establish the structure of **18** by ¹H NMR spectroscopy because the chemical shifts for the two sets of ring methylene hydrogens are coincident. Compound **18** is, however, a beautifully crystalline solid, and its constitution could be confirmed by X-ray crystallography. It is instructive to note that the product from this easily executed Diels–Alder reaction already has much in common with the targeted A-ring intermediate **11**.

It was recognized at an early stage that a C-1 keto function would permit an evaluation of a number of possibilities for joining A- and C-ring intermediates. At this stage in the synthesis, it was therefore necessary to address the problem of achieving the hydrolysis of the chloronitrile moiety in **18** to the corresponding ketone. Although several methods, including Evans's sodium sulfide method,¹⁴ were examined for this purpose, Shiner's protocol¹⁵ was found to be the most satisfactory. Thus, subjection of **18** to the action of five equivalents of potassium hydroxide in *tert*-butyl alcohol at 70 °C results in the formation of hydroxyketone **19** in 65% yield. Under these conditions, the hydrolysis of the chloronitrile moiety is accompanied by cleavage of the primary acetate group. Although the yield for this transformation is somewhat low and occasionally capricious, multigram quantities of hydroxyketone **19** can be prepared via this straightforward two-step sequence.



14: 2-chloroacrylonitrile



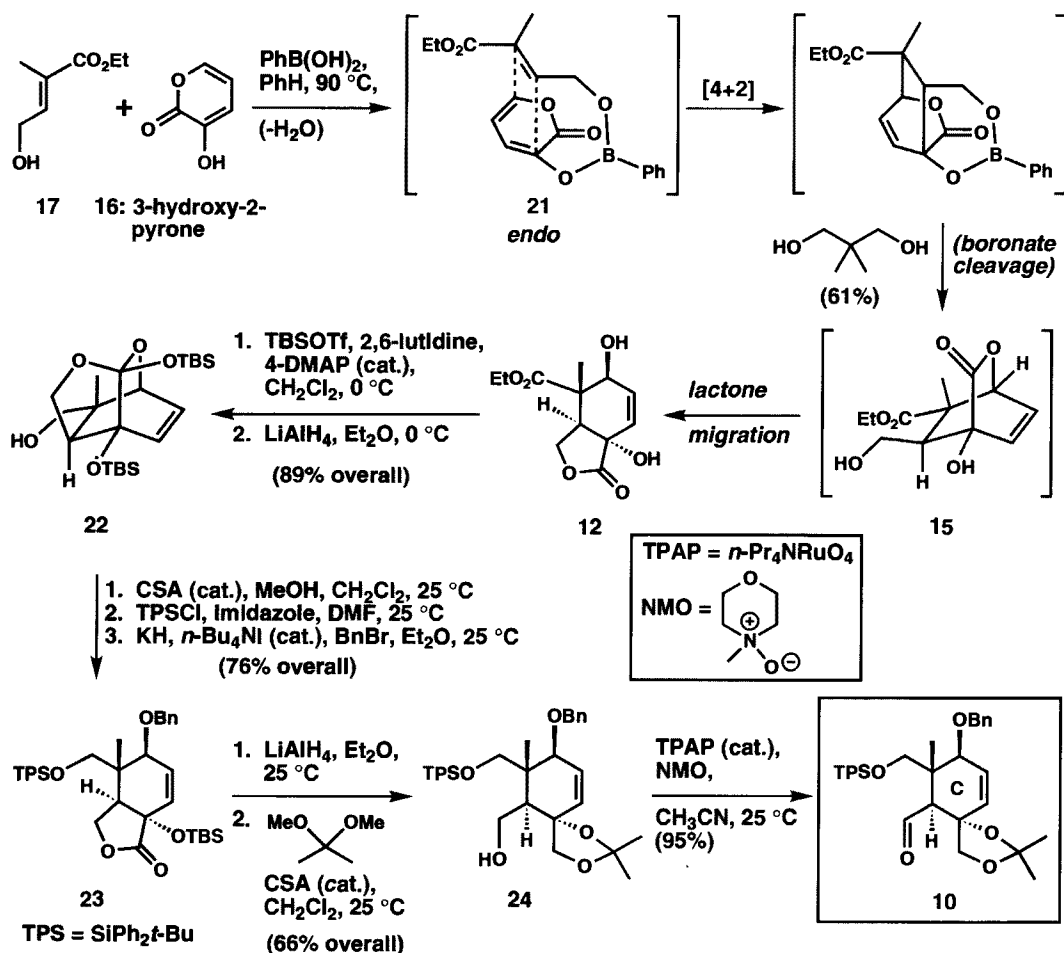
A digression is in order at this point. A fruitful by-product of research in organic synthesis has been the development of reagents that are *synthetically equivalent*¹⁶ to chemical species that are either inaccessible or are susceptible to undesirable reaction pathways. For example, a particularly direct approach to the synthesis of unsaturated ketone **20** would feature an intermolecular [4+2] cycloaddition reaction between a suitably protected diene and ketene. Unfortunately, however, ketene itself is not a viable dienophile in Diels–Alder reactions, because instead it participates in [2+2] cycloaddition reactions with 1,3-dienes to give substituted cyclobutanones. Thus, the identification of reagents that can serve as synthetic equivalents of ketene¹⁷ and can participate in Diels–Alder reactions with 1,3-dienes has significantly expanded the repertoire of organic synthesis. The ketene equivalent featured in Scheme 2 is 2-chloroacrylonitrile (**14**). This substance was selected for use in this synthesis because it has been shown to undergo highly regioselective cycloadditions with 1,3-dienes^{14,17,18} and because it is commercially available. Compound **14** is synthetically equivalent to ketene because the carbonyl group can be unveiled upon hydrolysis of the chloronitrile adduct (see **18** → **19**). It is as if ketene were employed in the Diels–Alder reaction.

Ketone **20**, derived in one uneventful step from hydroxyketone **19** (see Scheme 2), is a versatile synthetic intermediate. By virtue of its keto group, compound **20** could, in principle, serve as an electrophile in conventional carbonyl addition reactions with various C-ring nucleophiles. On the other hand, the keto function in **20** could provide a convenient handle for the elaboration of an A-ring nucleophile that could subsequently be joined with C-ring electrophiles. As matters transpired, many attempts to utilize **20** as an electrophile were thwarted by its pronounced tendency to enolize in the presence of nucleophilic (and basic) organometallic reagents. The latter option (A-ring as a nucleophile) was, however, found to be feasible. Despite its highly hindered (neopentyl) nature, the ketone carbonyl group in **20** reacts smoothly with 2,4,6-triisopropylbenzenesulfonylhydrazine¹⁹ to give crystalline hydrazone **11**. This substance is particularly interesting because it could conceivably be converted into vinyl lithium reagent **9** (see Scheme 1) via a Shapiro reaction.²⁰ Indeed, during the course of relevant model studies,²¹ it was found that putative vinyl lithium reagent **9**, derived from the action of *n*-butyllithium on hydrazone **11**, can be intercepted by model C-ring aldehydes.

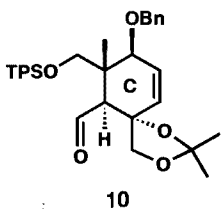
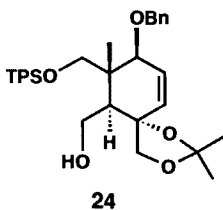
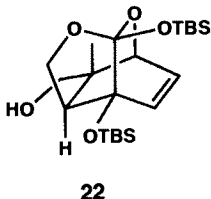
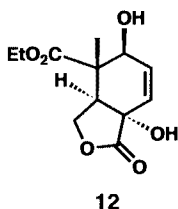
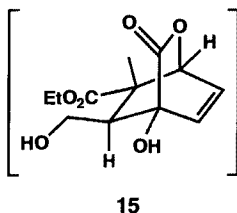
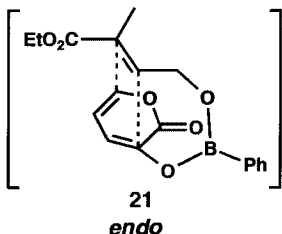
Of the two cyclohexenoid sectors of taxol, C-ring intermediate **10** is clearly the more complex (see Scheme 1). The cyclohexene ring in **10** includes four contiguous asymmetric carbon atoms, one of which is quaternary.²² When confronted with a highly stereodefined six-membered ring, one should be mindful of opportunities afforded by the powerful Diels–Alder reaction. Indeed, an important virtue of the Diels–Alder reaction is that it can create, in a single stereospecific step, a cyclohexene ring containing up to four contiguous stereogenic centers.¹² The Diels–Alder reaction is

considered stereospecific because relative stereochemical relationships contained within the diene and/or the dienophile are reflected in the [4+2] adduct; this is the familiar *cis* principle. In addition to its stereospecificity, the Diels–Alder reaction, in many instances, can be highly regio- and stereoselective.

A careful assessment of the constitution of compound **10** led to the development of a rather efficient strategy featuring the Diels–Alder reaction (see Scheme 3). Although the unassisted intermolecular reaction between 3-hydroxy-2-pyrone (**16**)²³ and α,β -unsaturated ester **17** is unacceptable in terms of both regioselectivity and chemical yield, compounds **16** and **17** combine smoothly in refluxing benzene and in the presence of phenylboronic acid to give fused bicyclic lactone **12** (61% yield) after workup with 2,2-



Scheme 3. Synthesis of aldehyde **10**.

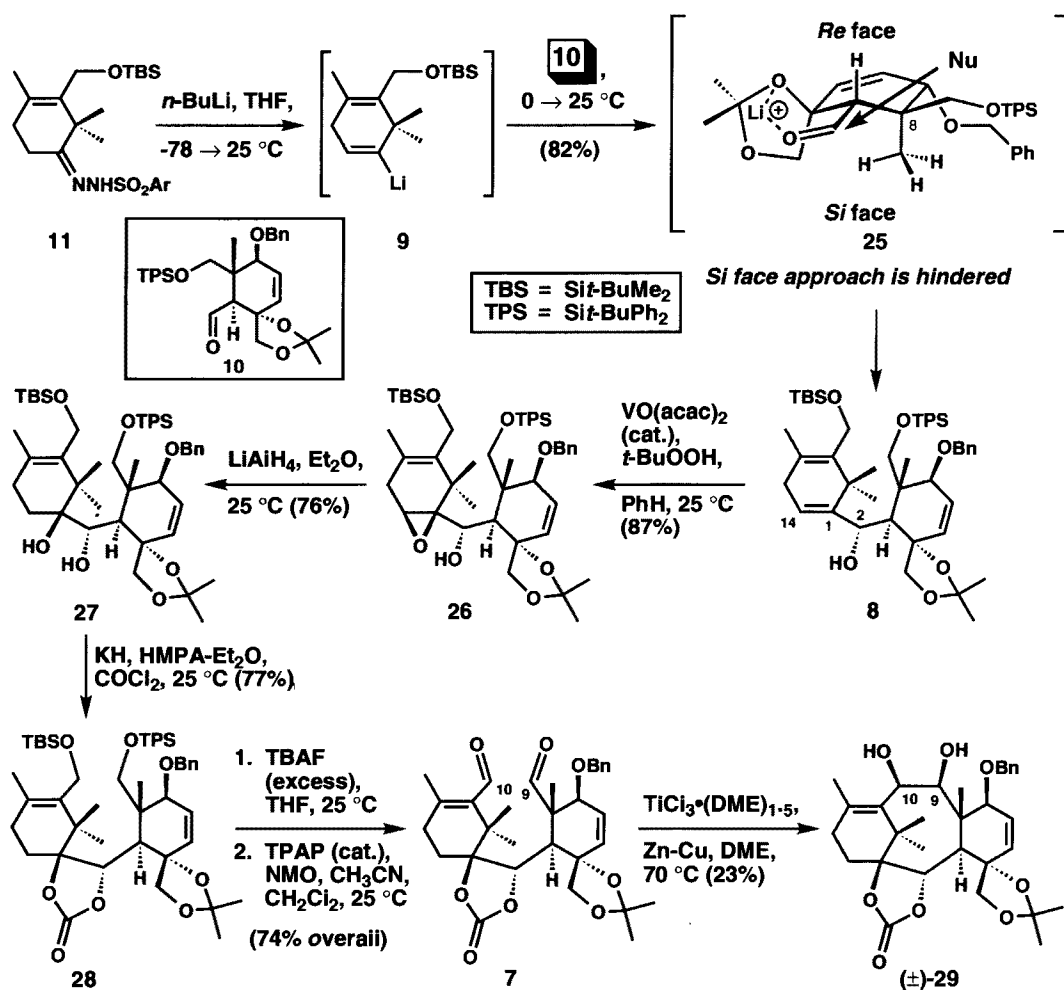


dimethyl-1,3-propanediol.²⁴ In this most productive reaction, which is based on the brilliant work of Narasaka,²⁵ these two simple achiral starting materials become linked to the boron atom of phenylboronic acid to give mixed boronate ester **21** after expulsion of two water molecules. The boron atom thus serves as a template and brings the diene and dienophilic components together to enable an intramolecular Diels–Alder reaction, thereby allowing the regiochemical course of the cycloaddition to be rigorously controlled. This transformation is among a diverse collection of reactions that are facilitated and controlled through the use of a disposable tether or atom.²⁶ Interestingly, bicyclo[2.2.2]lactone **15**, the expected product from this reaction, participates in a lactone migration reaction to give bicyclo[4.3.0]lactone **12**. It is noteworthy that Narasaka's boron template methodology enforces the union of compounds **16** and **17** and permits the construction of a molecule already possessing four of the requisite five contiguous stereogenic centers. In addition, the cycloaddition process exhibits complete *endo* stereoselectivity. Although **12** is prepared in racemic form, it possesses all the desired relative stereochemical relationships.

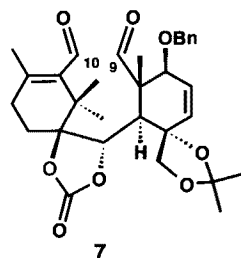
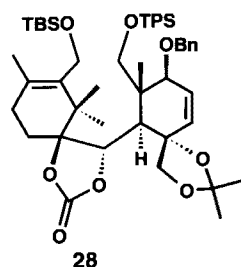
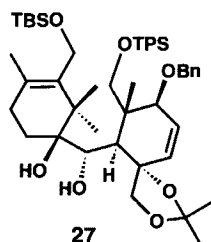
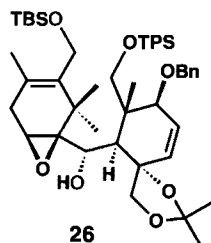
Bis(silylation) of **12** with excess *tert*-butyldimethylsilyl triflate (see Scheme 3), followed by a chemoselective reduction with lithium aluminum hydride (LiAlH_4) unexpectedly affords alcohol **22** in 89% overall yield. Exposure of **22** to a catalytic amount of camphorsulfonic acid (CSA) in methanol– CH_2Cl_2 selectively cleaves one the *tert*-butyldimethylsilyl ethers, providing a γ -lactone 1,3-diol in 94% yield. Sequential protection of the primary hydroxyl group as a *tert*-butyldiphenylsilyl ether (92% yield) and the secondary hydroxyl group as a benzyl ether (88% yield) proceeds smoothly under standard conditions without complications to furnish γ -lactone **23**. Reduction of the γ -lactone function in **23** with LiAlH_4 is accompanied by cleavage of the tertiary *tert*-butyldimethylsilyl ether to give the corresponding triol which can subsequently be converted to **24** on treatment with 2,2-dimethoxypropane and a catalytic amount of CSA (66% overall yield). Finally, oxidation of primary alcohol **24** with tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine-*N*-oxide (NMO)²⁷ takes place smoothly to give the desired C-ring aldehyde **10** (95% yield).

The development of the efficient reaction sequences summarized in Schemes 2 and 3 accomplished the first goal of the project. With appropriately functionalized and differentiated surrogates of taxol's A- and C-rings in hand, it was then necessary to contend with the potentially difficult task of effecting their union. You will note that compounds **10** and **11** are complementary with respect to reactivity. By virtue of the Shapiro reaction,²⁰ A-ring hydrazone **11** can be regarded as a latent carbon nucleophile. It was anticipated at the outset that the action of *n*-butyllithium on **11** would furnish vinyl-lithium reagent **9** (see Scheme 1), and that this reactive carbon nucleophile might then participate in a carbonyl addition reaction with aldehyde **10**. If successful, this convergent coupling reaction would accomplish the formation of the C1–C2 bond of taxol. In the

event, treatment of a solution of hydrazone **11** in THF with 2.1 equivalents of *n*-butyllithium at -78°C produces, after warming to 25°C , putative vinyl lithium reagent **9** (see Scheme 4).²⁸ Exposure of this reactive species to C-ring aldehyde **10** then results in the formation of allylic alcohol **8** (82% yield). Remarkably, compound **8** is the only stereoisomer observed in this reaction. This most gratifying result certainly was not predicted. The exclusive production of **8** in this manner is consistent with the addition of nucleophile **9** to the less hindered *Re* face of a chelated aldehyde carbonyl (see **25**); presumably the disposition of the C-8 methyl group would significantly hinder an addition to the *Si* diastereoface.



Scheme 4. Synthesis of intermediate (\pm)-**29**.



This coupling reaction is noteworthy for two reasons. First, it permits the union of the two sectors of taxol through a carbon-carbon bond between positions 1 and 2. Second, it affords an allylic alcohol, the hydroxyl group of which provides a convenient opportunity to selectively functionalize the $\Delta^{14,1}$ double bond. Treatment of a solution of **8** in benzene at 25 °C with *tert*-butyl hydroperoxide and a catalytic amount of VO(acac)₂ affords, as the sole product, epoxy alcohol **26** (87 % yield). In this successful Sharpless oxidation reaction,²⁹ the C-2 hydroxyl group in **8** directs, via a conformation that minimizes destabilizing nonbonding interactions between the two heavily substituted six-membered rings, a completely regio- and stereoselective epoxidation of the C14-C1 double bond.³⁰ The subsequent reductive opening of the oxirane ring in **26** with lithium aluminum hydride is also regioselective, affording vicinal diol **27** in 76 % yield. It is important to note that this three-step reaction sequence (i.e. coupling, oxidation, reduction) permits the construction of a key carbon-carbon bond and allows the vicinal oxygens at carbons 1 and 2 to be correctly positioned in space.

As discussed previously, the use of a cyclic protecting group bridging the vicinal hydroxyls at C-1 and C-2 is an important feature of this synthesis. It was hoped that this device would facilitate the pending pinacol coupling reaction by conferring conformational rigidity to the cyclization precursor (see intermediate **7**, Scheme 1). This tactic, together with the discovery that the C-1 hydroxy, C-2 benzoate system of the natural product can be unveiled in one step upon treatment of a simple cyclic carbonate with phenyllithium (see Figure 1), led to the selection of a carbonate as the cyclic protecting group. Treatment of a solution of diol **27** in HMPA-Et₂O at 25 °C with potassium hydride and phosgene results in the formation of carbonate **28** (77 % yield). Cleavage of both silicon protecting groups with excess tetra-*n*-butylammonium fluoride then furnishes a diol that can be easily oxidized to key intermediate **7** with TPAP-NMO²⁷ (74 % overall yield).

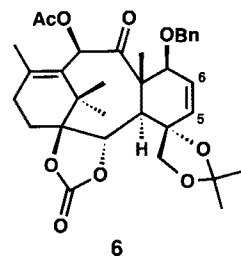
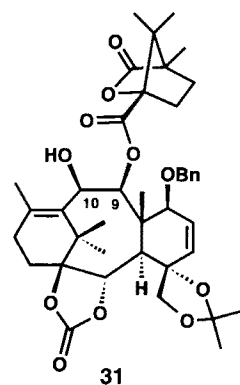
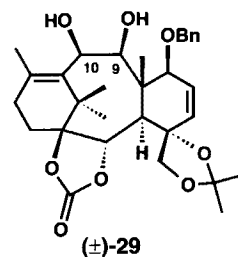
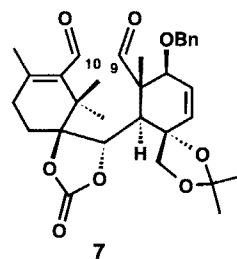
A critical stage in the synthesis has been reached. The constitution of dialdehyde **7** would seem to lend itself to a reductive carbonyl coupling reaction. If feasible, such a process would accomplish the construction of taxol's strained eight-membered ring, and it was hoped that carbons 9 and 10 would not, at any stage during the course of their union, be deprived of their valuable oxygen atoms. A Ti⁰-mediated pinacol coupling, also known as the McMurry coupling reaction, appeared particularly attractive. It is appropriate at this point to acknowledge important precedent that encouraged the selection of this particular cyclization reaction. In 1986, Kende and his collaborators disclosed a convergent synthesis of a rather advanced tricyclic taxane triene via a strategy that features a McMurry coupling reaction.³¹ Although the yield for the crucial cyclization step was modest (23 % yield), it was encouraging that the congested taxane carbon framework could be assembled through direct closure of the eight-membered B-ring. Moreover, refinements of and further insights into the McMurry coupling reaction were

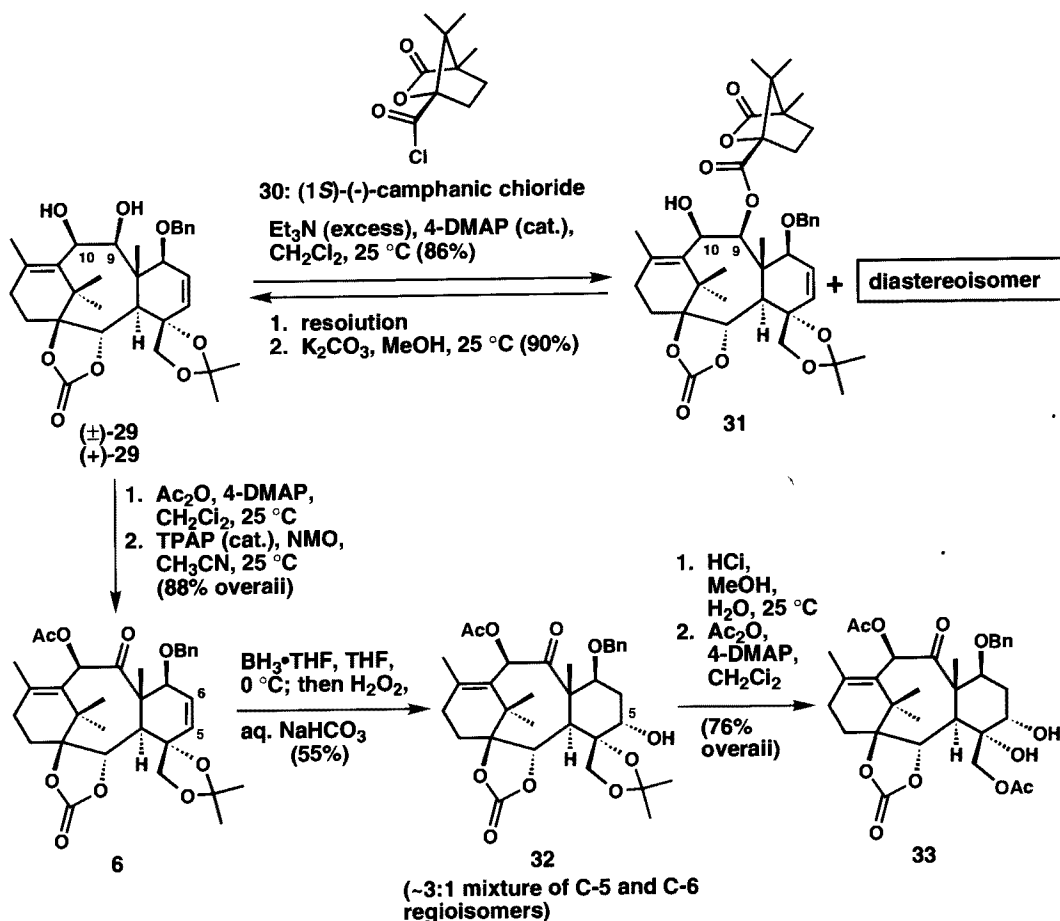
reported after Kende's disclosure, including several exciting uses of low valent Ti-induced ring closures in the context of natural product syntheses.³² For example, the final step in Dauben's elegant synthesis of (\pm)-kempene-2³³ is a McMurry cyclization of a keto aldehyde that possesses other potentially reducible functional groups. In retrospect, the successful applications of the McMurry coupling reaction for the construction of a taxane derivative by Kende³¹ and in numerous natural product total syntheses^{32,33} reinforced the decision to utilize the McMurry cyclization in this synthesis.

Through the reaction sequences described, gram quantities of dialdehyde **7** could be procured. As a result, the crucial McMurry pinacol coupling could be evaluated carefully so that optimum conditions for ring closure could be defined. After a good deal of systematic study, it was found that addition of dialdehyde **7** (in DME) by syringe pump to a solution of $\text{TiCl}_3 \cdot (\text{DME})_{1.5}$ (11 equivalents) and Zn–Cu couple (26 equivalents) in DME at 70°C results in the formation of *cis*-diol (\pm)-**29** in 23% yield. The rather low yield in this reaction reflects the inherent difficulties in forming highly functionalized and strained medium rings. Fortunately, sufficient quantities of (\pm)-**29** could be accumulated so that the synthesis could continue.

Although the diastereoselective transformations summarized in Scheme 4 have secured correct relative stereochemical relationships, all of the chiral intermediates described thus far are racemic. We were cognizant of the possibility that our racemic synthetic material could be resolved after the introduction of an enantiomerically pure taxol side chain. Nonetheless, the vicinal hydroxyl groups in (\pm)-**29** presented a very convenient opportunity to carry out a resolution at this stage of the synthesis. To this end, addition of (1*S*)-(-)-camphanic chloride (**30**)^{21b,34} to a solution of (\pm)-**29** and triethylamine in CH_2Cl_2 affords an equimolar mixture of C-9 camphanate diastereomers (**31** + diastereoisomer, 86% total yield) (see Scheme 5). The selective derivatization of the apparently more hindered C-9 hydroxyl in this reaction is somewhat surprising. Gratifyingly, the 1:1 mixture of monacamphanate diastereoisomers can be resolved chromatographically and, on the basis of an X-ray crystallographic analysis, it was possible to assign absolute stereochemistry to both isomers. The action of basic methanol on camphanate ester **31** cleaves the ester linkage and liberates stereoisomerically pure diol (+)-**29** (90% yield).

Whereas treatment of (\pm)-**29** with camphanic chloride achieves the selective esterification of the hindered C-9 hydroxyl group, the action of acetic anhydride on (+)-**29** results in the equally selective acetylation of the C-10 hydroxyl group! It is not clear to what this discrepancy should be attributed, so we will not offer a rationalization here. This unexpected result is, however, most gratifying because TPAP–NMO oxidation²⁷ of the remaining C-9 hydroxyl furnishes keto acetate **6** (88% overall yield). You will note that the contiguous keto and acetate functions in **6** are both expressed in the natural product.



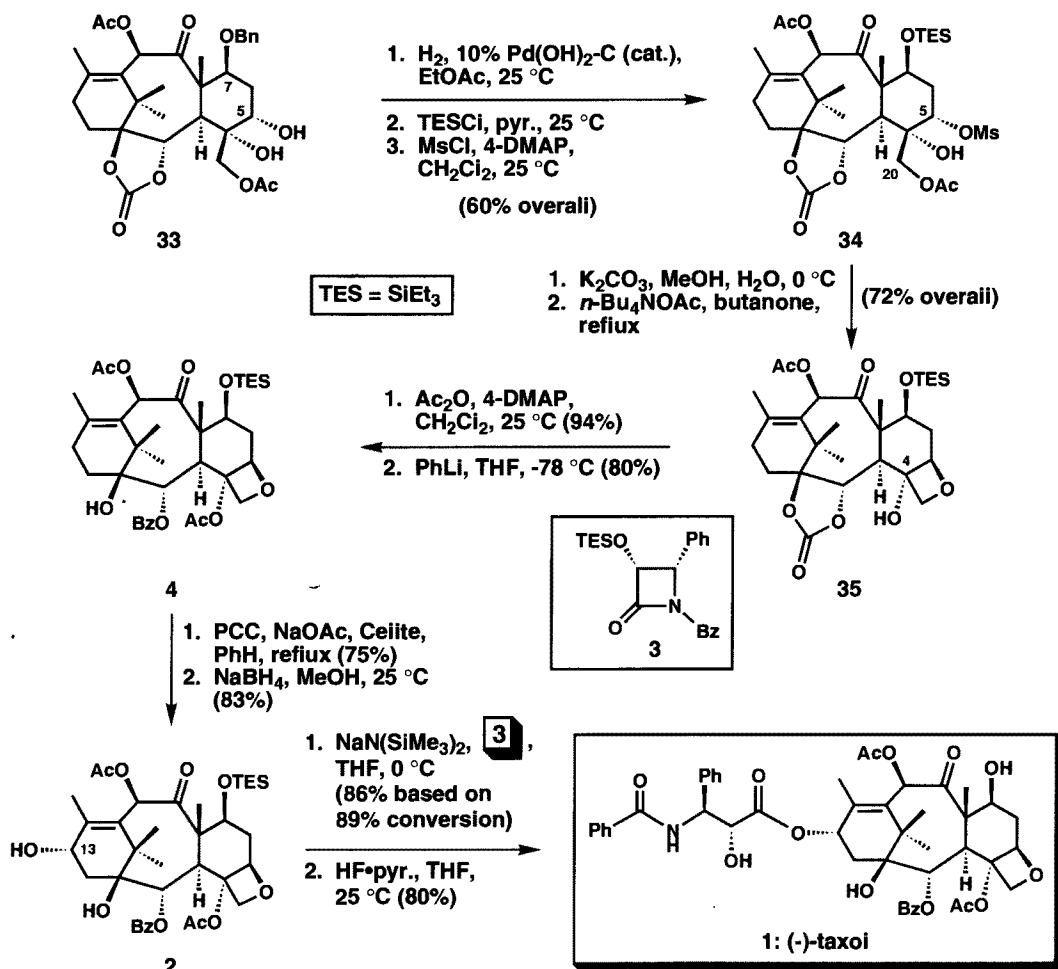


Scheme 5. Resolution of intermediate (±)-**29** and synthesis of intermediate **33**.

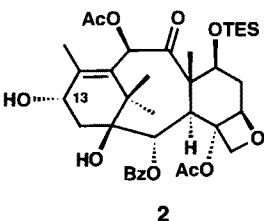
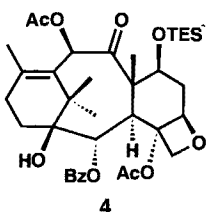
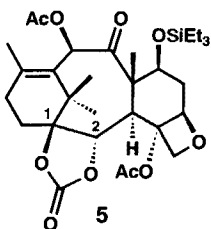
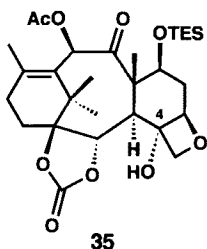
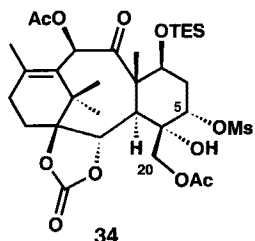
With an adequate solution to the B-ring problem, the unresolved issues associated with ring C can now be addressed. Intermediate **6**, containing an appropriately placed double bond, seems poised for the requisite oxetane annulation. As it turns out, the C-ring problem was approached from many different vantage points, and many unsuccessful experiments were performed. Nonetheless, it was eventually found that intermediate **6** could be converted into **32** through an intermolecular hydroboration/oxidation reaction (see Scheme 5). In the event, treatment of **6** with excess $\text{BH}_3\cdot\text{THF}$, followed by a standard oxidative workup, furnishes a 3:1 mixture of C-5 and C-6 alcohol regioisomers in favor of the desired alcohol **32** (55% total yield + recovered starting material). While the stereochemistry of the C-6 regioisomer remains unassigned, that of

the C-5 *a* isomer was established by conversion to and correlation with a degradation product. From intermediate **32**, the construction of the oxetane ring only requires a few functional group manipulations. Cleavage of the isopropylidene ketal in **32** with HCl in methanol, followed by selective acetylation of the primary hydroxyl group, furnishes intermediate **33** in 76% overall yield.

Hydrogenolysis of the C-7 benzyl ether, followed sequentially by selective triethylsilylation of the newly liberated C-7 hydroxyl and mesylation of the C-5 secondary hydroxyl, provides compound **34** in 60% overall yield (see **33** → **34**, Scheme 6). On the basis of Potier's studies,³⁵ it was hoped that the C-20 hydroxyl group,



Scheme 6. Synthesis of taxol (**1**).



derived from cleavage of the C-20 acetate in **34**, could be induced to displace the proximal C-5 mesylate in an intramolecular fashion. To this end, selective cleavage of the C-20 acetate in **34** can be brought about with basic methanol at 0 °C to give the desired diol mesylate. When a solution of the latter substance and excess tetra-*n*-butylammonium acetate in butanone is heated to reflux, the desired intramolecular etherification reaction takes place, with inversion of configuration at C-5, to give hydroxy oxetane **35** in 72 % yield. Despite its hindered nature, the C-4 tertiary hydroxyl group in **35** can be acetylated smoothly with acetic anhydride and 4-dimethylaminopyridine (4-DMAP) to give compound **5** (see Scheme 1) in 94 % yield.

Throughout the course of this synthesis, the five-membered carbonate ring has served several important functions. In addition to its passive role as a protecting group, the carbonate ring confers rigidity to pinacol cyclization precursor **7** and forces the two aldehyde carbonyls into reasonably close proximity; although an examination of molecular models suggested that this should have a very favorable effect on the cyclization event, there is certainly room for improvement in this most crucial stage. It was also anticipated, on the basis of chemical degradation/reconstitution studies, that the carbonate ring could also serve as a direct precursor to taxol's C-1 hydroxy and C-2 benzoate functions (see Figure 1). Indeed, treatment of compound **5** with phenyllithium at -78 °C in THF furnishes, in 80 % yield, the desired hydroxybenzoate ester **4** (Scheme 6). It is certainly noteworthy that the other three carbonyl groups and the oxetane ring are impervious to the action of phenyllithium under these conditions. The compatibility of the C-9 keto function, the two acetate esters, and the oxetane ring with this transformation presumably reflects the highly effective steric shielding that these groups experience within the crowded taxoid framework.

All that remains before the final destination is reached is the introduction of the C-13 oxygen and attachment of the side chain. A simple oxidation of compound **4** with pyridinium chlorochromate (PCC) provides the desired A-ring enone in 75 % yield via a regioselective allylic oxidation. Sodium borohydride reduction of the latter compound then leads to the desired 13 α -hydroxy compound **2** (83 % yield). Sequential treatment of **2** with sodium bis(trimethylsilyl)amide and β -lactam **3** according to the Ojima-Holton method³⁶ provides taxol bis(trimethylsilyl ether) (86 % yield, based on 89 % conversion) from which taxol (**1**) can be liberated, in 80 % yield, by exposure to HF•pyridine in THF at room temperature. Thus the total synthesis of (-)-taxol (**1**) was accomplished.

34.4 Conclusion

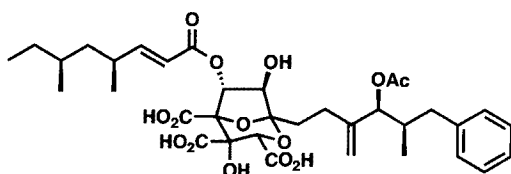
Taxol stood for more than two decades as a challenge to synthetic chemists, pointing out the weakness of the science of organic synthesis to construct highly oxygenated and congested polycyclic frameworks. With this synthesis and those reported by the Holton⁷ and Danishefsky⁸ groups a major barrier has been overcome and new vistas opened. A large number of designed taxol analogs were synthesized through application of the technology developed in this synthesis, and new strategies and tactics for chemical synthesis were established. Amongst the most interesting features of this route to taxol are: (a) the boron-mediated Diels–Alder reaction to provide an entry into the highly functionalized C-ring framework; (b) application of Shapiro and McMurtry reactions to couple the two ring systems and effect closure of the eight-membered ring; and (c) the regio- and stereocontrolled incorporation of the oxygen functionalities in the eight-membered ring of taxol.

Of course, one should realize that, while the approach described above appears to have proceeded smoothly, much unsuccessful but often interesting work remains untold in this chapter. For a number of unsuccessful attempts, the reader is referred to the original papers,^{6,11,13,21a,b,24} but even there much of the drama and excitement remains obscure. Only those who were there at the time will ever know the entire story.

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1: zaragozic acid A / squaliastatin S1

K. C. Nicolaou (1994)

Zaragozic Acid A / Squaliastatin S1

35.1 Introduction

In most industrialized nations, coronary heart disease (CHD) is the largest single cause of death, causing more fatalities than all forms of cancer combined.¹ As such, it is a very expensive disease, with an estimated annual cost in the U.S. alone of \$20 billion from health care costs, disability, and lost productivity (1991 figures).¹ Consequently, in recent years intensive efforts have been funded by many governments to search for ways of reducing coronary illnesses. One of the main causes of CHD is atherosclerosis, a disease commonly known as “hardening of the arteries”, which is characterized by the formation of fatty plaques of cholesterol, lipids, and other cellular debris in the arteries. In much the same fashion as water pipes in a heating system “fur-up” with old age, the cross-sectional area of the artery is reduced, the flexibility of the artery wall is diminished, and the heart is forced to work much harder as a consequence. Although the exact pathogenesis of atherosclerosis is not known, there is a clear positive correlation between the incidence of CHD and elevated serum cholesterol levels.² Many Western nations have embarked on extensive educational programs to encourage people to eat healthier foods, but this provides only a partial, if very effective, solution. This is because the human body obtains only about half of its requirement for cholesterol from the diet: the rest is biosynthesized endogenously, mainly in the liver.

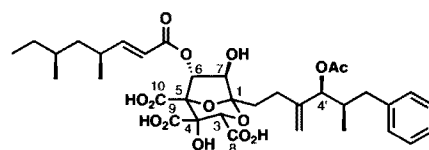
The biosynthetic pathways for sterol biosynthesis have been known for a long time and a brief summary is presented in Scheme 1.³ Starting from acetyl CoA (**2**), acetoacetyl CoA, and

The search for inhibitors of this pathway began with the first key regulatory enzyme, HMG CoA reductase. Several clinically useful inhibitors of HMG CoA reductase are now known. One of the most successful, Mevacor, produced by Merck, is one of the pharmaceutical industry's best selling products. However, the problem with inhibiting a *branched* biosynthetic pathway at an early point is that the biosynthesis of other crucial biomolecules may also be inhibited. Indeed, there is some evidence that levels of ubiquinone and the dolichols are affected by some HMG CoA reductase inhibitors. Consequently, efforts have recently been directed towards finding inhibitors of squalene synthase, the enzyme controlling the first step on the route to cholesterol *after* the FPP branch point.

Medicinal chemistry has frequently drawn inspiration and important new leads from the examination of natural products, and this was proven to be the case once more. In 1992, researchers at Merck and Glaxo announced, almost simultaneously, the independent discovery of the same new class of natural products from two different fungi. As a consequence, the same family of natural products has two names – the zaragozic acids (Merck)⁴ or the squalostatins (Glaxo).⁵ A typical member of the family, zaragozic acid A (squalestan S1) (**1**) was shown to have a tremendous affinity for squalene synthase ($K_i = 79 \text{ pM}$ for rat microsomal squalene synthase) and could even lower serum cholesterol levels *in vivo* in a population of marmosets.⁶

From a structural standpoint the central tricarboxylic acid “core” is the most interesting portion of the zaragozic acids; it is common to all members: the others differ only in the nature of the alkyl side chain at C-1 and the ester side chain at C-6. The core is very heavily oxygenated, quite unprecedented, and offered a significant synthetic challenge. This, together with their amazing biological activity, made the zaragozic acids exciting targets for synthesis in the early 1990s. Later in this chapter, we describe the Nicolaou synthesis of zaragozic acid A (**1**).⁷ The keynote of this synthesis was the use of the Sharpless Asymmetric Dihydroxylation (AD) reaction,⁸ a process still in its infancy but which promises to be a powerful tool for the synthesis of complex oxygenated molecules.

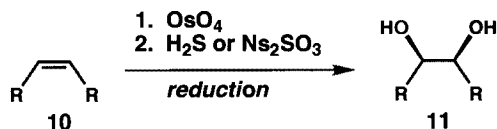
In the following sections and before we describe the synthesis of zaragozic acid A, we give a brief historical introduction to the dihydroxylation reaction, then describe the development of the Sharpless AD and some of its recent applications.



1: zaragozic acid A

35.1.1 The Asymmetric Dihydroxylation

The *cis* dihydroxylation of olefins (**10**→**11**, Scheme 2), one of organic chemistry's most venerable reactions, was first reported by Makowaka in 1908.⁹ It is also one of the most useful reactions, since it converts an olefin, itself a pivotal functional group, to a vicinal diol, another pivotal functional group present in many natural products and unnatural molecules. The original dihydroxyl-



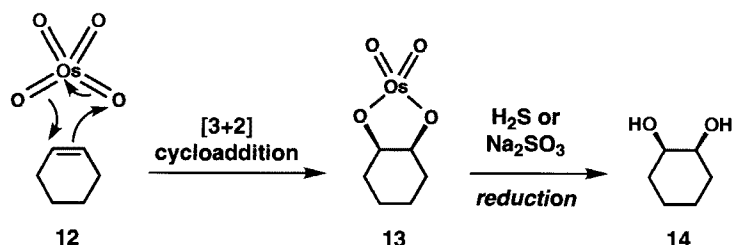
Scheme 2. The osmium tetroxide mediated dihydroxylation reaction.

ation¹⁰ used stoichiometric amounts of osmium tetroxide (OsO₄), which is expensive, volatile, and toxic, with the result that even small-scale reactions were far from convenient. However, its specificity for double bonds – *only* double bonds but *all* double bonds – was quickly recognized and remains the reaction's most commented-upon feature. Furthermore, the dihydroxylation has no particular substrate requirements (e. g. the directing effect of an adjacent heteroatom), which increases its applicability still further.

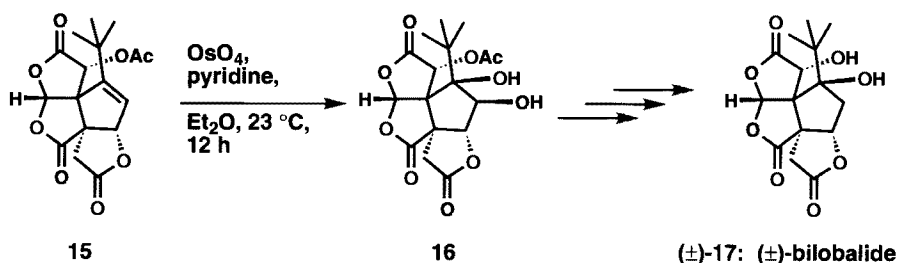
Over the years, the original dihydroxylation procedure has been modified to operate catalytically, more rapidly, and in better yield. However, the last remaining task, making the dihydroxylation of a prochiral olefin *enantioselective* without losing all the other desirable features of the reaction, has only recently become a reality.

It is perhaps surprising that methods for the conversion of olefins to diols with only catalytic amounts of osmium tetroxide and a stoichiometric cooxidant have been known almost as long as the reaction itself.^{11,12} The stoichiometric dihydroxylation of olefins with OsO₄ has always been reliable; even tetrasubstituted double bonds react reasonably well. Criegee first observed that the addition of amines, such as pyridine, to the dihydroxylation reaction increases its rate,¹³ presumably by formation of an electron-rich coordination complex with the osmium atom. A simple mechanistic rationale for the stoichiometric dihydroxylation is shown in Scheme 3; an alternative proposal by Sharpless will be discussed briefly later (Scheme 12). It was postulated that the olefin (e. g. **12**) undergoes a [3+2] cycloaddition with OsO₄ to give the osmate(vi) glycolate ester **13**. The glycolate **13** is stable and can be isolated and characterized. Reduction, usually with H₂S or Na₂SO₃, gives the diol **14**. Although this is generally an excellent reaction, the expense incurred in stoichiometric dihydroxylation reactions has precluded its use in all but the most crucial situations. One of these is represented in Corey's synthesis of the ginkgolide compound, (±)-bilibalide [(±)-**17**] (see **15** → **16**, Scheme 4).¹⁴

The first OsO₄-cooxidant combinations appear to be the Hofmann reagent, OsO₄-MClO₃ (M = Na, K),¹⁰ and later improvements (M = Ag, Ba) by Braun.¹⁵ Although there have been substantially better methods for some time, these conditions are still occasionally used in undemanding situations. The other classical method, Milas's reagent (OsO₄-H₂O₂), is also still used, but over-oxidation is frequently a problem and yields are sometimes low.

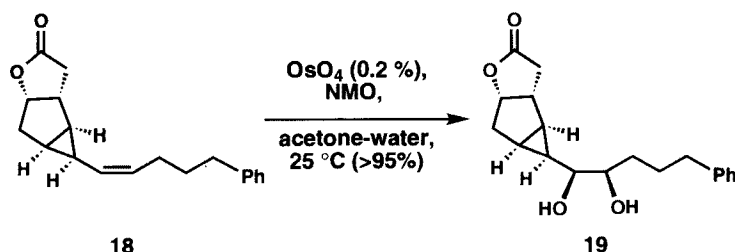


Scheme 3. The Criegee mechanism for the osmium tetroxide mediated dihydroxylation reaction.

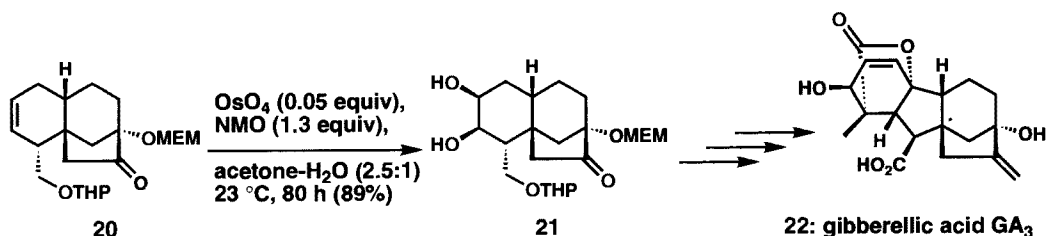


Scheme 4. Corey's synthesis of (±)-bilobalide [(±)-17], employing a stoichiometric osmium tetroxide mediated dihydroxylation reaction.

In the first significant improvement in the nature of the stoichiometric oxidant, Sharpless¹⁶ employed *tert*-butyl hydroperoxide (TBHP) and a base such as tetraethylammonium hydroxide or tetraethylammonium acetate in *tert*-butanol or acetone. These conditions minimized over-oxidation and yields were frequently superior to those obtained with the Hoffman or Milas reagents. However, the best stoichiometric oxidant, and certainly the one most widely used at present, is *N*-methylmorpholine *N*-oxide (NMO), discovered by workers at Upjohn during the synthesis of a prostaglandin (see **18** \rightarrow **19**, Scheme 5).¹⁷ The Upjohn process, as it is now often referred to, uses similarly modest amounts of osmium tetroxide (0.2–1%), over-oxidation is almost completely suppressed, and yields are frequently quantitative. Consequently, it has been used in many natural product syntheses including Corey's synthesis of gibberellic acid GA₃ (**22**) (see **20** \rightarrow **21**, Scheme 6)¹⁸ and Nicolaou's synthesis of zaragozic acid A⁷ (see **82** \rightarrow **84**, Scheme 20). The most recent addition to the list of secondary cooxidants is potassium ferricyanide/potassium carbonate [K₃Fe(CN)₆–K₂CO₃], introduced by Yamamoto in 1991.¹⁹ This reagent combination had a profound effect on the development of the Sharpless AD (*vide infra*).



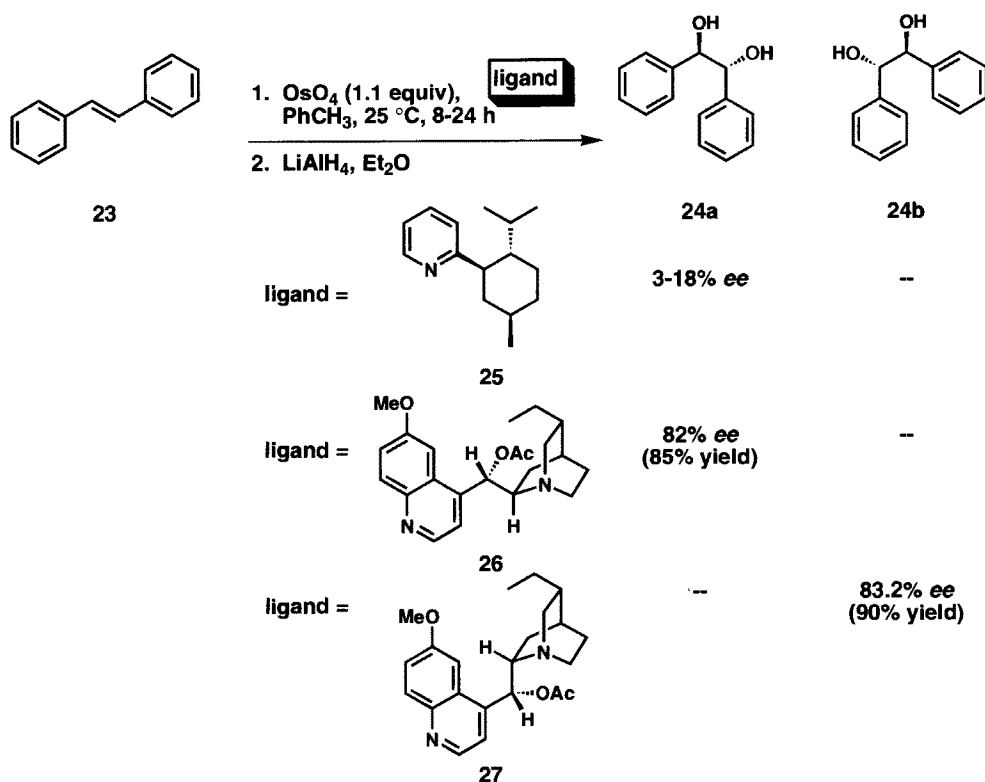
Scheme 5. Upjohn's catalytic dihydroxylation process with OsO_4 and 4-methylmorpholine *N*-oxide (NMO).



Scheme 6. Corey's synthesis of gibberellic acid GA_3 (**22**) employing the Upjohn catalytic dihydroxylation procedure.

The interest in asymmetric synthesis that began at the end of the 1970s did not ignore the dihydroxylation reaction. The stoichiometric osmylation had always been more reliable than the catalytic version, and it was clear that this should be the appropriate starting point. Criegee had shown that amines, pyridine in particular, accelerated the rate of the stoichiometric dihydroxylation, so it was understandable that the first attempt at nonenzymatic asymmetric dihydroxylation was to utilize a chiral, enantiomerically pure pyridine and determine if this induced asymmetry in the diol. This principle was verified by Sharpless (Scheme 7).²⁰ The pyridine **25**, derived from menthol, induced *ee*'s of 3–18% in the dihydroxylation of *trans*-stilbene (**23**). Nonetheless, the *ee*'s were too low and clearly had to be improved.

In the same paper, Sharpless²⁰ disclosed that the presence of the large chiral group close to the pyridine nitrogen (the site of coordination) reduced the affinity of the pyridine for the osmium, which meant that the ligand probably was absent from the osmium atom for many of the dihydroxylations. Griffith²¹ had shown that tertiary amines (e.g. quinuclidine) have a much higher affinity for osmium than pyridines, so chiral quinuclidines **26** and **27** (Scheme 7), derived from the family of naturally occurring cinch-

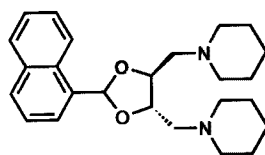
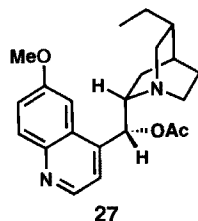
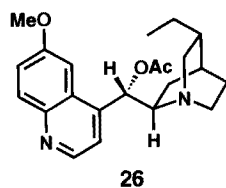


Scheme 7. The first enantioselective dihydroxylation reactions (developed by Sharpless).

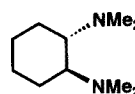
ona alkaloids, were tried instead. There are a large number of tertiary amines in the chiral pool, and fortunately it was recognized to be important to choose one for which the enantiomer was also readily available. Because the dihydroquinine (DHQ) alkaloid **26** and the dihydroquinidine (DHQD) alkaloid **27** are not exactly enantiomeric, having the same configuration at the relatively remote C-3 and C-4 stereocenters, they are often called *pseudo-enantiomers*. These two alkaloids have a chiral center directly adjacent to the site of coordination – one atom closer than the pyridine **25** – which augured well for asymmetric induction. These projections proved correct; dihydroxylation of *trans*-stilbene (**23**) with ligand **26** gave, after reduction of the osmate ester with LiAlH_4 in ether, diol **24a** in 82% ee^{20,22} (Scheme 7). The other enantiomer, **24b**, could be obtained in similar yield and ee simply by utilizing ligand **27** instead of **26**. Other olefins representing four of the six possible substitution patterns were tested and gave diols with ee's ranging from 6–83% and yields of 62–90%.

A logical extension of this idea, and an extension of the success of the C_2 -symmetric bidentate ligands used in other asymmetric applications, was to create bidentate amine ligands to chelate the Osmium(VIII) species. A number of research groups²³ adopted this approach – Narasaka's was the first^{23a} in 1986 – with considerable success. In most instances, the *ee*'s ranged up to 99 % *ee* for *trans*-stilbene, one of the most favorable substrates for the dihydroxylation reaction. Some of the ligands are shown in Figure 1.

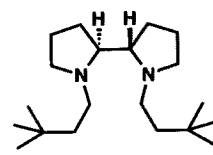
The next development was of course to make the dihydroxylation catalytic with respect to osmium tetroxide (and ideally the ligand). Although the bidentate ligands generally induced higher *ee*'s than Sharpless's monodentate cinchona alkaloid ligands **26** and **27**, making them apparently more suitable for investigation of the catalytic asymmetric dihydroxylation, the reason for the success of the bidentate ligands also proved to be the reason for their demise. The chelate effect²⁴ meant that the bidentate ligands bound very strongly to the osmium atom, causing the osmium(VI) glycolate intermediate to be quite resistant to hydrolysis, and preventing its reentry into the catalytic cycle. The corollary is, of course, that a more weakly binding ligand (such as the cinchona alkaloid type) is more likely to result in greater turnover, but with lower *ee*, through dihydroxylation of the olefin with an uncomplexed osmium atom.



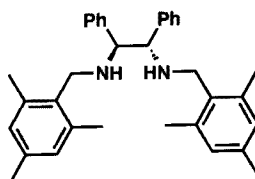
Narasaka (1986)



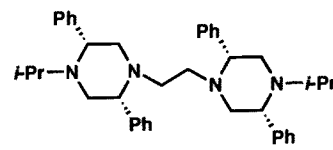
Snyder (1986)



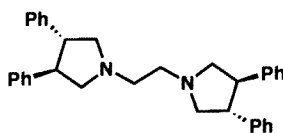
Hirama (1989)



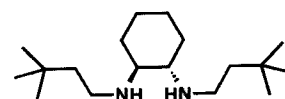
Corey (1989)



Fuji (1992)



Tomioka (1993)



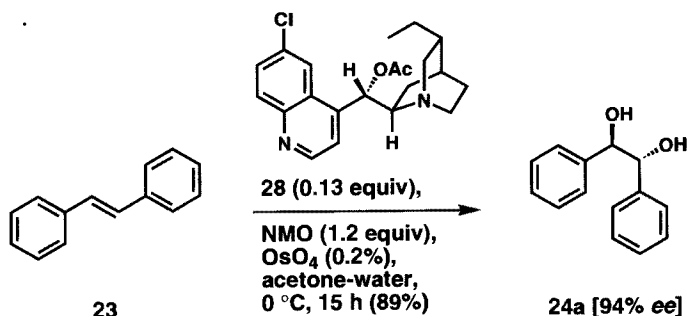
Hanessian (1993)

Figure 1. Selected bidentate ligands used in the stoichiometric asymmetric dihydroxylation (AD).

This is all neatly summed up in the concept of “ligand-accelerated catalysis”:²² if a chiral ligand can activate a catalyst so that it is only significantly active when bound as a catalyst–ligand complex, then all the product from the reaction will have arisen through reaction with this complex and asymmetric induction will have been maximized. Thus, the best solution is a compromise: a catalyst–ligand complex that is tight enough to accelerate reaction with the substrate, but one that is not too tight to slow down subsequent steps in the catalytic cycle. The original pyridine ligand **25** failed the first criterion; the bidentate ligands in Figure 1 fulfilled the first, but failed the second; the cinchona alkaloid ligands **26** and **27** (Scheme 7) appear to be just right.

It is not surprising, therefore, that in the very same paper in which the concept of ligand-accelerated catalysis was introduced,²² the results of the first *catalytic* asymmetric dihydroxylation were also disclosed. The seemingly trivial marriage of the Sharpless cinchona alkaloid stoichiometric dihydroxylation process, now optimized with ligand **28**, with the practical qualities of the Upjohn NMO procedure resulted in good yields (8–95%) for a range of diols in moderate to good enantiomeric excesses (20–88%) with as little as 0.2% of the osmium catalyst (Scheme 8). Over the next four years, four substantial improvements were made to the AD: (1) the change of the stoichiometric oxidant from NMO to $\text{K}_3\text{Fe}(\text{CN})_6\text{--K}_2\text{CO}_3$; (2) a method for effecting a general increase in the rate of reaction; (3) a new class of “dimeric” ligands combining two alkaloid units linked by an aromatic “spacer” unit; and (4) a more convenient source of osmium(VIII).

The reason for the decrease in the enantiomeric excess observed in changing from stoichiometric to catalytic conditions was demonstrated to be due to a second catalytic cycle in which the chiral



Scheme 8. The first catalytic asymmetric dihydroxylation (developed by Sharpless).

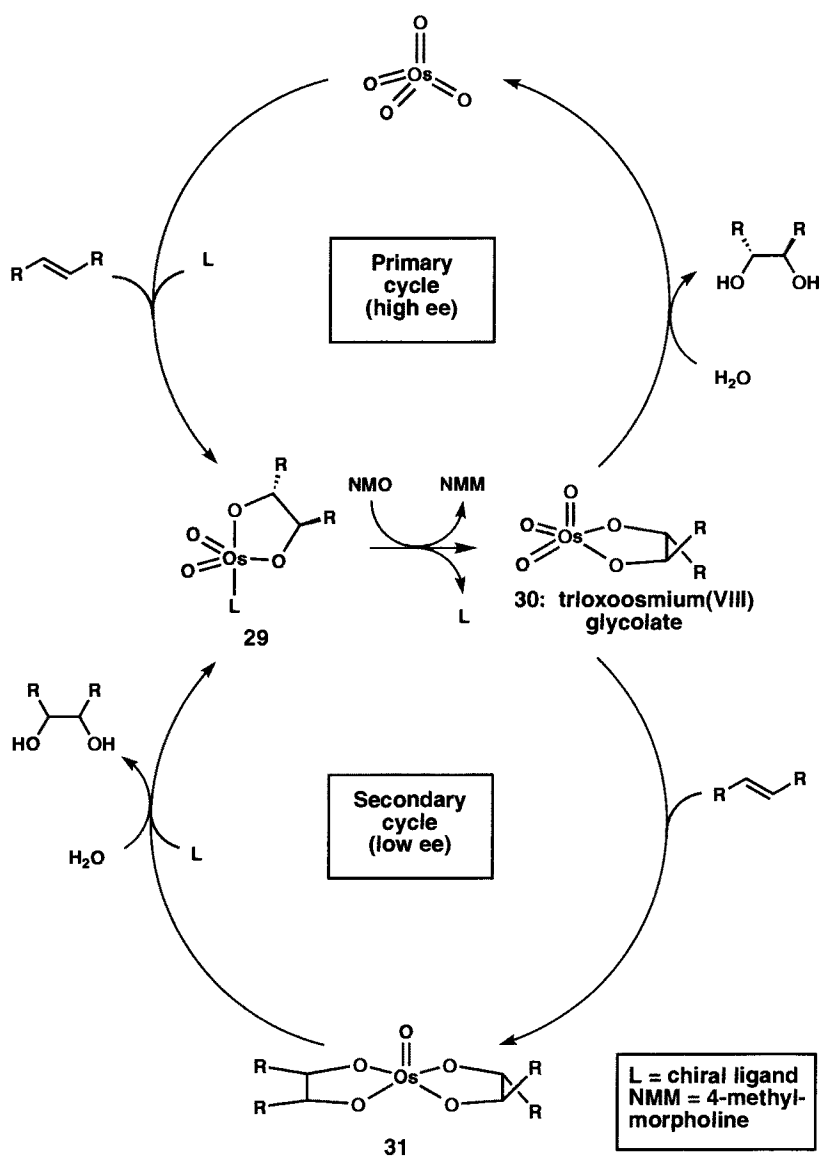
ligand is not involved (see Scheme 9).²⁵ This involved oxidation (in the homogenous reaction mixture) of the initially formed Os^{VI} glycolate **29** to the Os^{VIII} glycolate **30**, with the loss of the chiral ligand L. This could then perform another, virtually nonenantioselective dihydroxylation to give the diglycolate **31**. However, when the catalytic system K₃Fe(CN)₆–K₂CO₃ in *t*-BuOH–H₂O is used,¹⁹ the oxidant is confined to the aqueous phase, allowing the osmium(vi) glycolate **29** to hydrolyze in the organic layer before being reoxidized. In practice, the *ee*'s obtained with K₃Fe(CN)₆ were uniformly higher than with NMO as the stoichiometric oxidant.

The low rate of reaction for trisubstituted olefins was shown to be a result of slow hydrolysis of the osmium glycolate **29**. However, this hydrolysis can be accelerated by a factor of up to 50 simply by the addition of methanesulfonamide.²⁶ This modification permits the AD to be performed at lower temperature, which nearly always results in an increase in the stereoselectivity of the reaction.²⁷

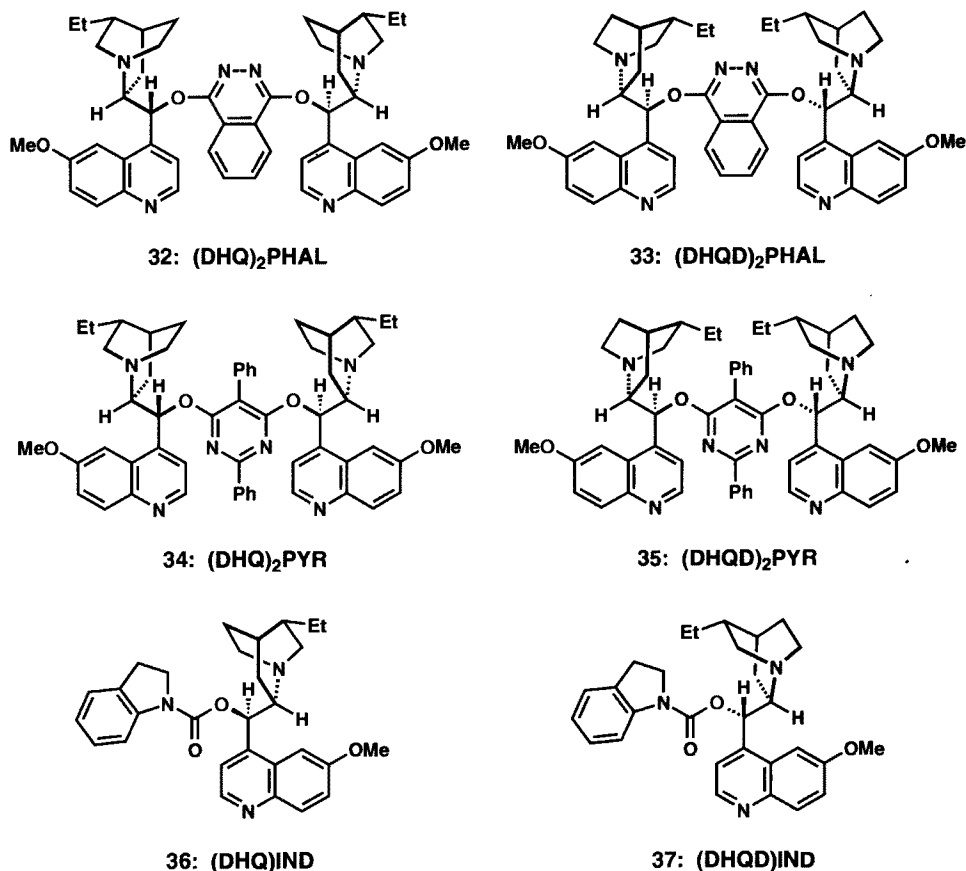
The third and very valuable discovery that the new phthalazine (PHAL) and pyrimidine (PYR) ligand classes (**32–35**, Figure 2) out-perform the monomeric ligands under identical conditions emerged from a heuristic screening process. The PHAL class in particular has become the first choice for most olefin classes. The PYR class is usually superior for terminal olefins, while the IND class is ideally suited for *cis*-disubstituted olefins. These ligands are commercially available or can be made easily from relatively inexpensive starting materials.

From a consideration of models of the reaction and knowledge of the absolute configuration of a number of products, an empirical “mnemonic device” has been proposed (see Figure 3).²⁶ This can be used to predict which pseudo-enantiomeric ligand should be used to obtain the desired enantiomer of the diol. So far, no exceptions have been found for simple olefins. To use the device, one evaluates which of the substituents on the olefin is the larger or largest. The olefin is then drawn in the device such that for example, the largest substituent is in the southwest corner. To dihydroxylate the bottom or *α*-face of the olefin, the (DHQ)₂PHAL ligand should be used; to construct the enantiomeric diol, (DHQD)₂PHAL is the choice. For olefins with substituents of comparable steric bulk, the prediction may be quite difficult. It is clear from the mnemonic device why the dihydroxylation does not work well with *cis*-disubstituted olefins, particularly when the two substituents are of similar size. In the limit, when the two substituents *are* the same size, the two faces of the olefin are identical, and the catalyst cannot distinguish between them.

Finally, it was discovered that dipotassium osmate dihydrate (K₂OsO₄•2H₂O) is a suitable replacement for OsO₄.²⁶ Gratifyingly, all of the necessary ingredients in the AD (catalyst system, oxidant, and ligand) are now solids and can be preformulated as two “cake mixes”, one for each enantiomer. It is now possible to buy “AD-mix *α*” (which contains (DHQ)₂PHAL, K₂OsO₄•2H₂O, K₃Fe(CN)₆,



Scheme 9. The two catalytic cycles for the Sharpless AD with NMO as a cooxidant.



reagents	(DHQ) ₂ PHAL	(DHQD) ₂ PHAL	K ₂ OsO ₂ (OH) ₄	K ₃ Fe(CN) ₆	K ₂ CO ₃
AD-mix α	5.52 g	--	0.52 g	700.0 g	294.0 g
AD-mix β	--	5.52 g	0.52 g	700.0 g	294.0 g

Figure 2. Structures of phthalazine (**32,33**), pyrimidine (**34,35**), and indoline (**36,37**) ligands used in the Sharpless AD and composition of AD-mix α and AD-mix β.

and K₂CO₃), and “AD-mix β” (the same, but with (DHQD)₂PHAL instead of (DHQ)₂PHAL, Figure 2). The formulation is such that all one has to do is to stir equal amounts of water and *tert*-butanol, 1.4 g of AD-mix per mmol of olefin, and the olefin itself at 0 °C until the reaction is complete (usually overnight). This straightforward recipe is beginning to reduce the commonly perceived “black art” of organic chemistry to a nearly embarrassing level of simplicity.

As discussed in Chapter 19, the concept of reagent control has revolutionized chemistry in the latter part of the 20th century. By

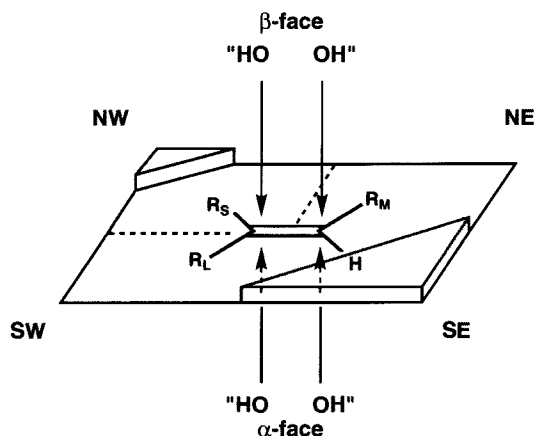
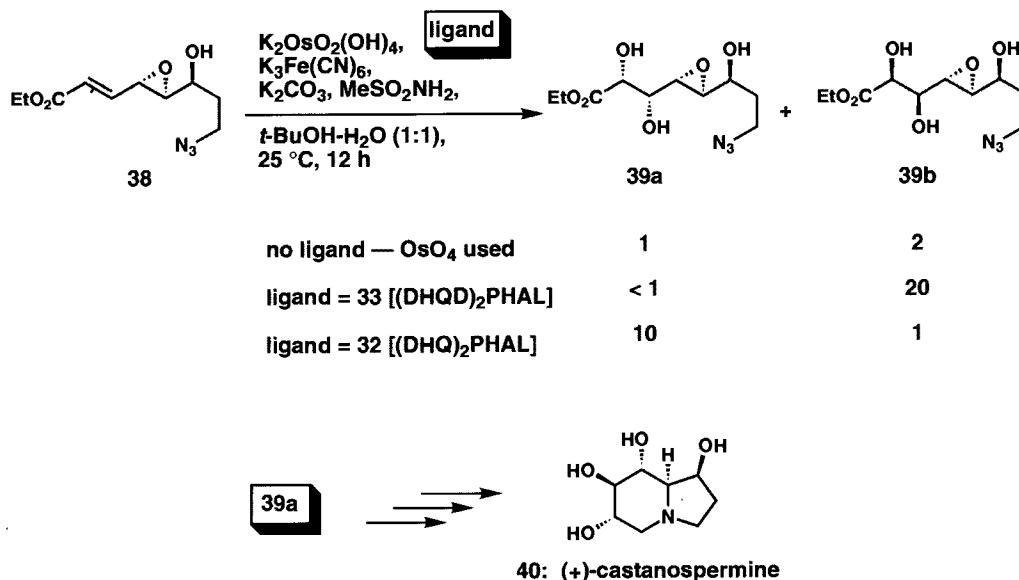
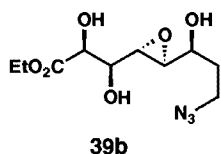
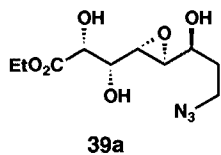
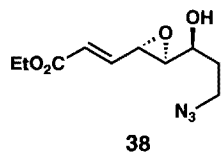


Figure 3. Mnemonic device for the AD of olefins [Ref. 8].

utilizing a powerful external source of enantiomerically pure chirality, it is possible, in principle at least, to overwhelm the inherent diastereofacial bias of a chiral substrate molecule. There are currently not many such examples of doubly diastereoselective AD, but one example that illustrates the principle and practice perfectly is shown in Scheme 10. Castanospermine (**40**), a glycosidase inhi-

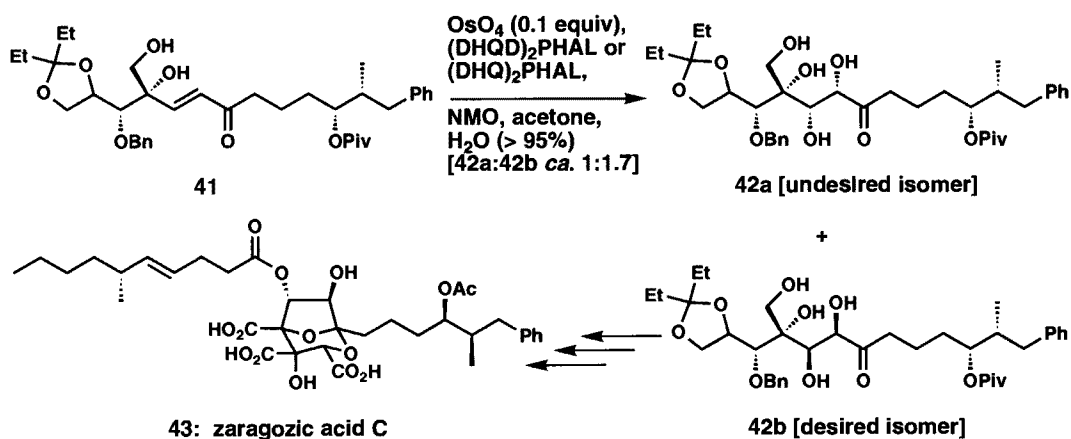


Scheme 10. Cha's synthesis of (+)-castanospermine (**40**).



bitor and long a benchmark test for new synthetic methodologies, was synthesized by Cha²⁸ from enantiomerically pure epoxide **38**. The substrate has a weak intrinsic bias (**39a**:**39b** = 1:2) that favors the production of diastereoisomer **39b** as evidenced from its reaction under standard dihydroxylation conditions. This preference is augmented to a ratio of 20:1 by the use of AD-mix β . The pairing of substrate **38** with (DHQD)₂PHAL constitutes a *matched* case, because the two components have the same stereofacial preference. However, AD-mix α is sufficiently powerful to overwhelm the intrinsic preference of **38** for **39b**, giving a 1:10 ratio of products in favor of **39a** (the *mismatched* case). The latter substance could then be converted to the natural product. This is an important feature, because it allows stereoselective syntheses to be planned with some confidence. One example where the AD is not diastereoselective is found in Carreira's synthesis²⁹ of zaragozic acid C (**43**) (Scheme 11). The olefin **41** gives almost equimolar mixtures of diols **42a** and **42b** with standard non-AD conditions, and with both AD-mixes. The major isomer **42b** was subsequently converted to zaragozic acid C.

A noteworthy feature of the Sharpless Asymmetric Epoxidation (SAE) is that kinetic resolution of racemic mixtures of chiral secondary allylic alcohols can be achieved, because the chiral catalyst reacts much faster with one enantiomer than with the other. A mixture of resolved product and resolved starting material results which can usually be separated chromatographically. Unfortunately, for reasons that are not yet fully understood, the AD is much less effective at kinetic resolution than the SAE.

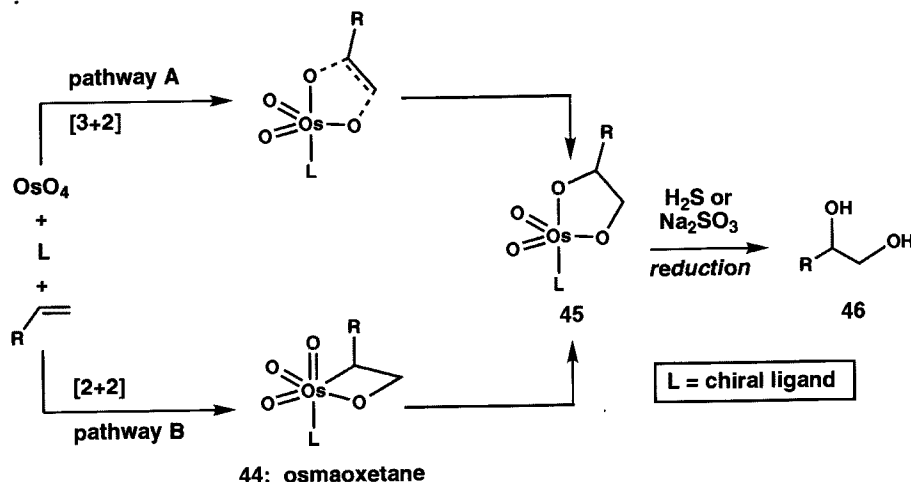


Scheme 11. Carreira's synthesis of zaragozic acid C (**43**).

The mechanism and the precise origin of the enantioselectivity of the AD remains an ongoing issue.⁸ The first mechanistic proposal for the dihydroxylation advanced by Criegee in 1936¹³ (Scheme 3) can be applied, in slightly revised form, to the AD (Scheme 12, pathway A). This suggestion initially involves a [3+2] cycloaddition of OsO_4 with an olefin to give directly the Os^{VI} glycolate ester **45**, which is then hydrolyzed, either as part of a catalytic cycle or stoichiometrically, to give the diol **46**. This postulate, appealing in its simplicity, accounts for the formation of the isolable Os^{VI} glycolate **45**, and has not yet been disproven.

However, in 1977 Sharpless³⁰ suggested the possibility that the Os^{VI} glycolate can be formed in a two-step process (pathway B, Scheme 12) *via* the osmaoxetane intermediate **44**. Initially a [2+2] cycloaddition occurs, followed in a second step by a stereospecific rearrangement to give the glycolate ester **45**. Despite efforts at determining which of these pathways is operating, no definite conclusions have yet been drawn. Nevertheless, recent analyses of the temperature dependence of the *ee*, and high level *ab initio* calculations suggest that the osmaoxetane pathway may be operating. The osmaoxetane pathway also has the intuitive appeal that the reaction of the olefin with the osmium–ligand complex occurs closer to, and directly with, the osmium atom, rather than solely with the oxygens on the periphery of the complex.

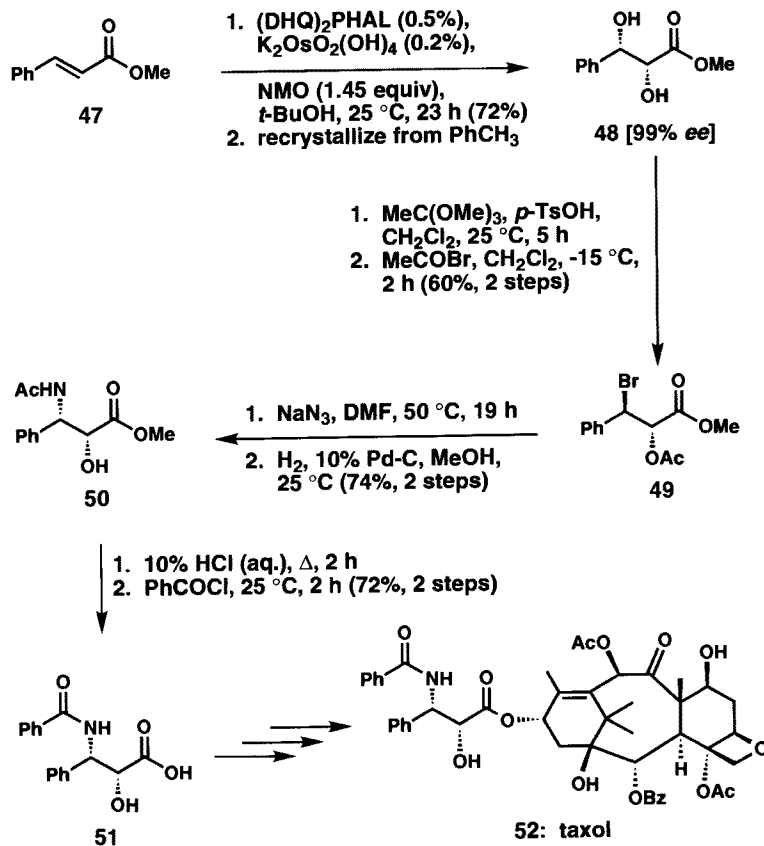
Since the 1992 publication by Sharpless,²⁶ more investigators have had the courage to try the AD. Many of the following examples are quite simple, but serve to illustrate certain important aspects of the AD. In many instances, the AD has shortened an



Scheme 12. Mechanistic alternatives: [2+2] vs. [3+2] cycloaddition of OsO_4 and an olefin.

existing synthetic sequence by many steps; in others, the remarkable regioselectivity has been an important feature. In all the examples, the practical convenience has been emphasized. At present, there are few natural product syntheses that utilize the AD; one exception is the Nicolaou synthesis of zaragozic acid A (**1**)⁷ which is discussed in the next section. There can be no doubt, however, that many more applications of the AD are certain to follow in the years ahead.

The total synthesis of taxol (**52**) has been described in Chapter 34. Clearly, total synthesis cannot hope to meet the demand for taxol at the present time, and supplies are currently procured by semisynthesis. This approach uses baccatin III (derived from yew tree needles) and the C-13 side chain **51**, made synthetically (Scheme 13). A practical synthesis of the side chain is necessary,

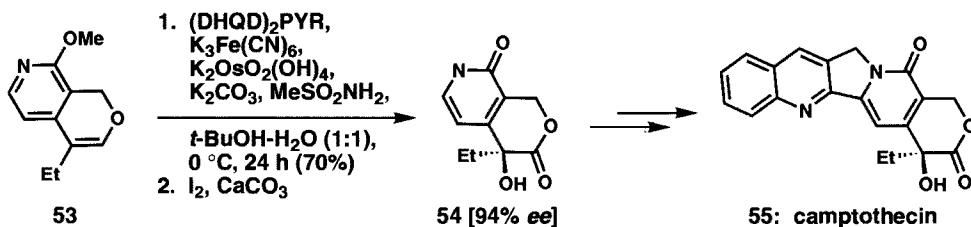
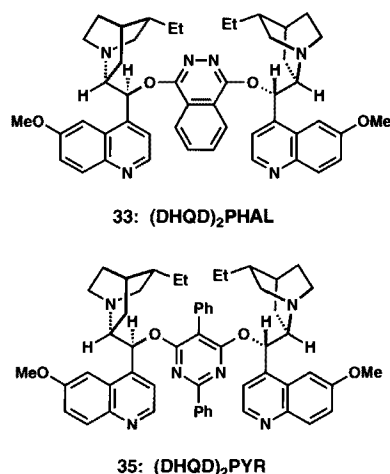


Scheme 13. Sharpless's asymmetric synthesis of the C-13 side chain **51** of taxol (**52**).

and the AD rises magnificently to the occasion.³¹ Starting with methyl cinnamate (**47**) (\$0.08 / g), AD furnishes the diol **48** in 72 % yield and 99 % *ee* after recrystallization. Although the original secondary oxidant, NMO, was used instead of $\text{K}_3\text{Fe}(\text{CN})_6\text{-K}_2\text{CO}_3$, which resulted in a slightly lower *ee*, the much higher concentration at which the reaction could be run more than compensated. Differentiation of the two hydroxyl groups of the diol – a potential problem in any application – can be achieved by forming a mixed ortho ester which can subsequently be opened regioselectively at the benzylic position by bromide ion to give the *anti* bromo acetate **49** (regioselectivity 6:1). Displacement of the bromide by $\text{S}_{\text{N}}2$ attack of azide with inversion of configuration, followed sequentially by reduction of the azide to the amine and transacylation affords acetamide **50**. Hydrolysis of the acetamide, benzoylation, and hydrolysis of the ester then gives the C-13 side chain **51** of taxol (**52**) in 23 % overall yield from **47**. In this manner, several moles of **51** can be made through a straightforward, cheap, and relatively environmentally safe process.

Camptothecin (**55**, Scheme 14) is an important anticancer agent. Researchers at Glaxo³² required large amounts of enantiomerically pure lactone **54**, which Comins³³ had previously shown could be converted to **55** in an efficient three-step procedure. This application of the AD not only illustrates the utility of the AD, but reminds us that the magic AD-mix powders do not always work the first time! Starting with 2-methoxypyridine, a series of standard manipulations provides the enol ether **53**. Standard AD with AD-mix β [which contains $(\text{DHQD})_2\text{PHAL}$ (**33**) as the chiral ligand] and MeSO_2NH_2 gave a slight preference for the desired enantiomer, but only in 26 % *ee*. However, by changing the ligand from $(\text{DHQD})_2\text{PHAL}$ (**33**) to $(\text{DHQD})_2\text{PYP}$ (**35**), the *ee* was increased to 94 %! At a stroke, large amounts of enantiomerically pure **54**, a crucial building block for camptothecin analogs, became available immediately.

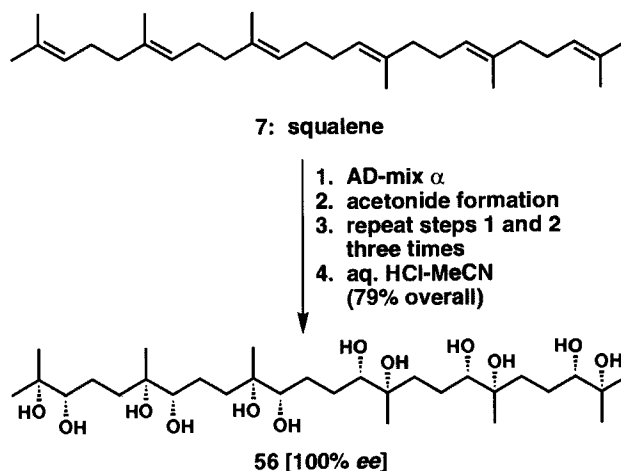
Squalene epoxidase, a key enzyme in the biosynthesis of cholesterol (**9**), epoxidizes one face of one of the three different olefins in squalene (**7**) to give squalene epoxide (**8**), which then cyclizes eventually to give cholesterol (**9**) (Scheme 1). The AD of squalene (**7**)



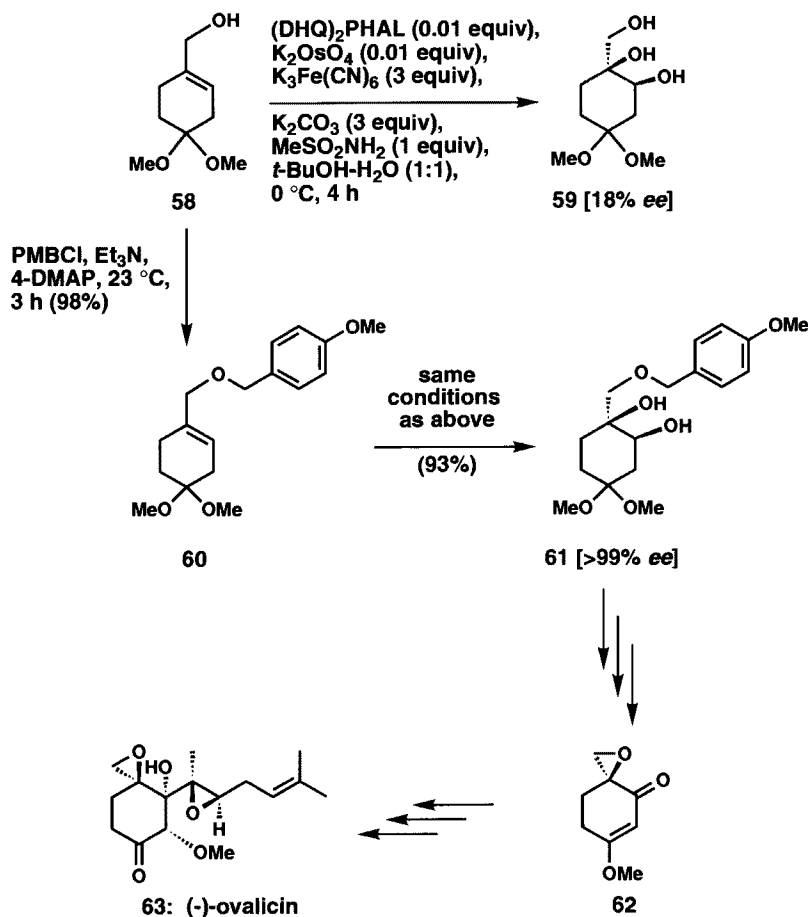
Scheme 14. Glaxo's formal asymmetric synthesis of camptothecin (**55**).

is not as regioselective, giving a mixture of diols, which are virtually enantiomerically pure. This feature was exploited in a synthesis of the perhydroxysqualene **56** (Scheme 15).³⁴ By treating squalene successively with three rounds of AD, followed by acetonide formation (to aid solubility), the enantiomerically pure dodecanol **56** was produced in 78.9% yield. Of the 36 possible isomers (including enantiomers) only one is formed; without the ligand, all isomers are formed in a statistical mixture. The six AD events (the first enantioselective, the rest diastereoselective) required to give perhydroxysqualene must each proceed with an average of 98% *ee* or *de* to give the observed yield of 78.9%. While not of immediate use, this example shows a transformation that would be virtually impossible to carry out by traditional chemical or enzymatic methods.

One way of inhibiting tumor growth is to cut off the tumor's blood supply by preventing angiogenesis, the process of new growth of blood vessels. Ovalicin (**63**, Scheme 16) inhibits angiogenesis, and this important biological finding prompted Corey and coworkers to resynthesize ovalicin, previously prepared as a racemate,³⁵ via optically active intermediate **62**.³⁶ Starting from *p*-methoxybenzyl (PMB) alcohol, **58** can be synthesized in three steps (Scheme 16). However, AD of **58** with (DHQD)₂PHAL as the chiral ligand, affords **59** in only 18% *ee*. Simply attaching a PMB group to the alcohol, to give ether **60**, dramatically increases the *ee* of the AD to >99%. This interesting result was attributed to attractive interactions between the PMB group and the aromatic units on the ligand. Enantiomerically pure **61** can be converted to intermediate **62** and thence to (–)-ovalicin (**63**) by using a previously established pathway.³⁵



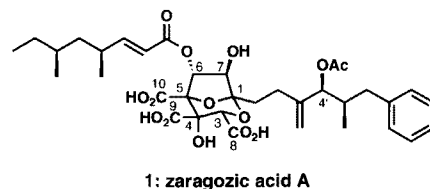
Scheme 15. Sharpless's perhydroxylation of squalene (**7**).

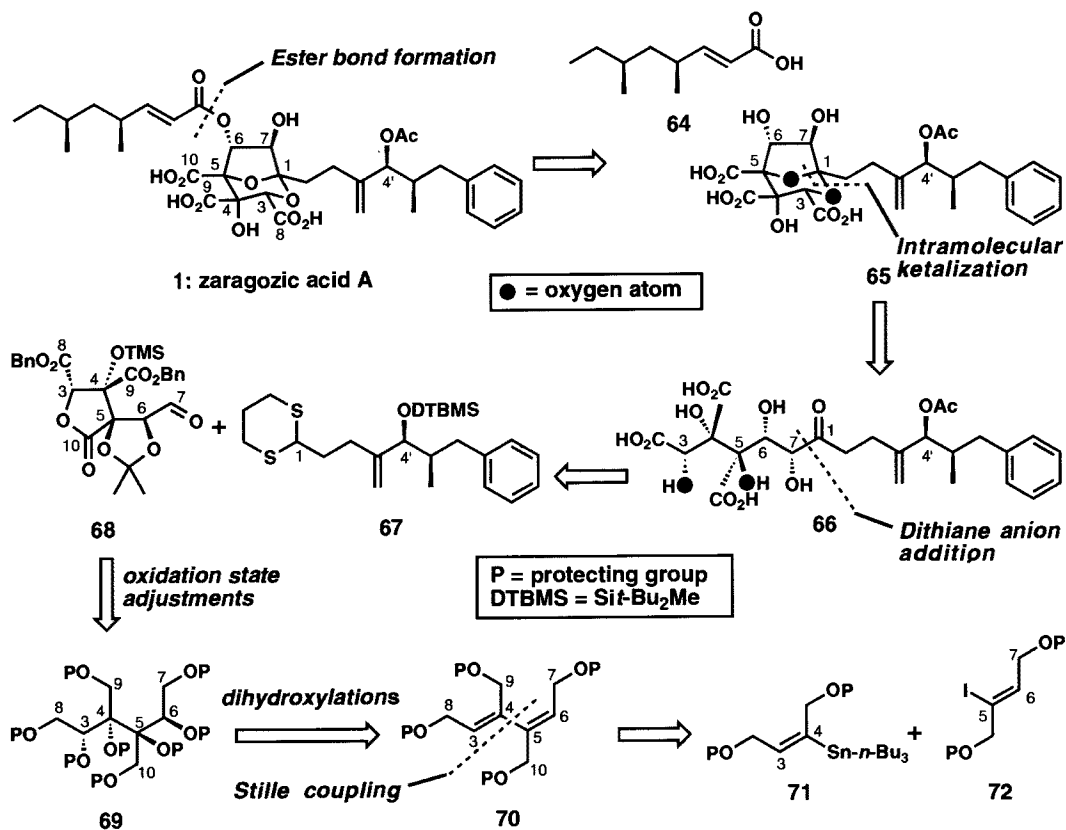


Scheme 16. Corey's synthesis of (-)-ovalicin (**63**).

35.2 Retrosynthetic Analysis and Strategy

Zaragozic acid A (**1**) contains three distinct domains: the C-6 acyl side chain, the C-1 alkyl side chain, and the bicyclic "core", its most striking feature. At the outset, it was clear that the key to a successful synthesis of zaragozic acid A lay in finding an effective synthesis of the highly oxygenated bicyclic core. A logical synthetic strategy would defer the introduction of the two side chains to a late stage in the synthesis, so that, in principle, a common intermediate representing the core could be used to assemble a range of zaragozic acids and analogs. The retrosynthetic analysis of the Nicolaou synthesis of compound **1** is shown in Scheme 17. Retrosynthetic removal of the C-6 acyl side chain **64** from zaragozic





Scheme 17. Retrosynthetic analysis of zaragozic acid A/squalestatin S1 (1).

acid A, the first disconnection, furnishes unsaturated carboxylic acid **64** and intermediate **65** as potential precursors.

The bicyclic core looks deceptively complicated. By imagining an acid-catalyzed ketalization, it was hoped that the bicyclic core might spontaneously self-assemble from the open-chain form **66**. This strategy is predicated on the notion that bicyclic ketal **65** is preferred on thermodynamic grounds, and that the required configuration at C-1 in **65** would arise naturally from an acid-catalyzed ketalization of **66** under equilibrating conditions. Such thermodynamically controlled ketalizations are commonplace in organic synthesis, particularly in the spiroketal field. The open-chain form **66** now looks rather less intimidating than its ketalized form and more like a familiar problem of acyclic stereocontrol. Cleavage of the C1–C7 bond in **66** yields two fragments of approximately equal size. The C-1 alkyl side chain is conveniently excised as the acyl anion equivalent, dithiane **67**, thus providing an excellent opportunity for late-stage convergency. It was also anticipated that the

α -alkoxy aldehyde **68**, which represents the bicyclic core structure, would impart some selectivity in the formation of the C-7 stereocenter, and that this could be achieved by fine-tuning the experimental conditions.

The next retrosynthetic task was to arrange for suitable protection of all the hydroxyl and carboxyl groups in **68** as economically as possible. By employing two cyclic protecting groups, the lactone and the acetonide, the protecting group strategy was simplified. Aldehyde **68** could conceivably derive from a general precursor of the type **69**, in which all the oxidation states have been reduced to the level of an alcohol. The intermediate **69** possesses two adjacent and central 1,2-diol functionalities (C3–C4 and C5–C6). The next disconnection, which seemed rather brave at the time, was to remove both of these dihydroxy groups to give the prochiral diene **70**. In the synthetic direction, it was planned to perform two dihydroxylations on diene **70**, the first enantioselective and the second diastereoselective. This double dihydroxylation strategy reduces the intimidating problem of the four contiguous stereocenters in **69** to the much easier problem of controlling the configuration of the double bonds in the diene **70**. Note that if the diene is appropriately presubstituted with oxygens at C-7, C-8, C-9, and C-10, then the two dihydroxylations introduce the remaining carbon–oxygen connectivity in only two simple steps. The synthesis is thus reduced to a technical matter of revealing the alcohols and the carboxyls at the appropriate times in the synthetic sequence to secure the correct oxidation states at all the right positions.

The constitution of diene **70** permits a powerful retrosynthetic maneuver. Retrosynthetic cleavage of the C4–C5 bond furnishes vinylstannane **71** and vinyl iodide **72** (see Scheme 17). This retrosynthetic step divides the eight backbone carbon atoms equally between two fragments, and takes advantage of the facility with which conjugated dienes can be constructed by the palladium-catalyzed Stille coupling reaction. It should be noted that the vinyl iodide and the vinylstannane both contain trisubstituted double bonds, which are notoriously difficult to construct with a high degree of stereoselectivity. Fortunately, the vinylstannane **71** contains two identical *cis* substituents and could potentially be assembled by a *cis*-hydrostannylation of the corresponding (symmetrical) alkyne. The advantage here is that a hydrostannylation of a symmetrical alkyne would not be plagued by regiochemical problems. With respect to compound **72**, it was our hope that a Wittig reaction between the stabilized ylide, $\text{Ph}_3\text{P}=\text{C}(\text{I})\text{CO}_2\text{Me}$, and a simple two-carbon aldehyde could be used to establish the configuration of the trisubstituted $\Delta^{5,6}$ double bond in **72**. This strategy has the advantage that by having the C-10 carbon atom in **70** at a higher oxidation state, a “handle” is attached to an otherwise highly symmetrical molecule.

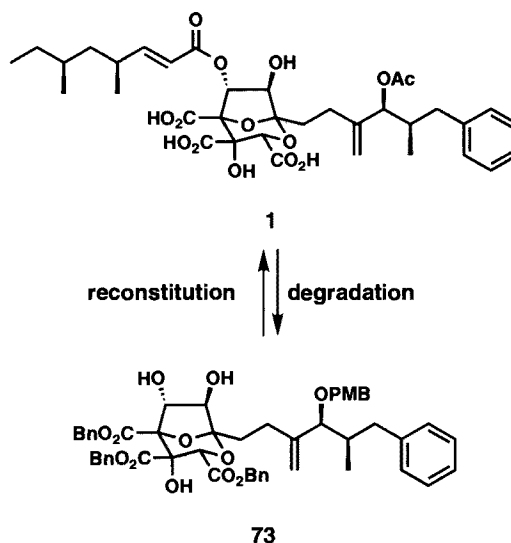
The retrosynthetic analysis described above outlines a triply convergent strategy towards the synthesis of zaragozic acid A (**1**). The most pleasing aspect of the retrosynthetic strategy is the rapid and enantioselective manner in which the “two-dimensional” molecule

70 is transformed into the complex, three-dimensional structure **68**. Nevertheless, the anticipated and aesthetically pleasing conversion of **66** to **65** also had the distinct possibility of catastrophic failure, and had to be investigated first on an appropriate model system. The successful execution of this strategy is outlined below.

35.3 Total Synthesis

35.3.1 Degradation and Reconstitution Chemistry

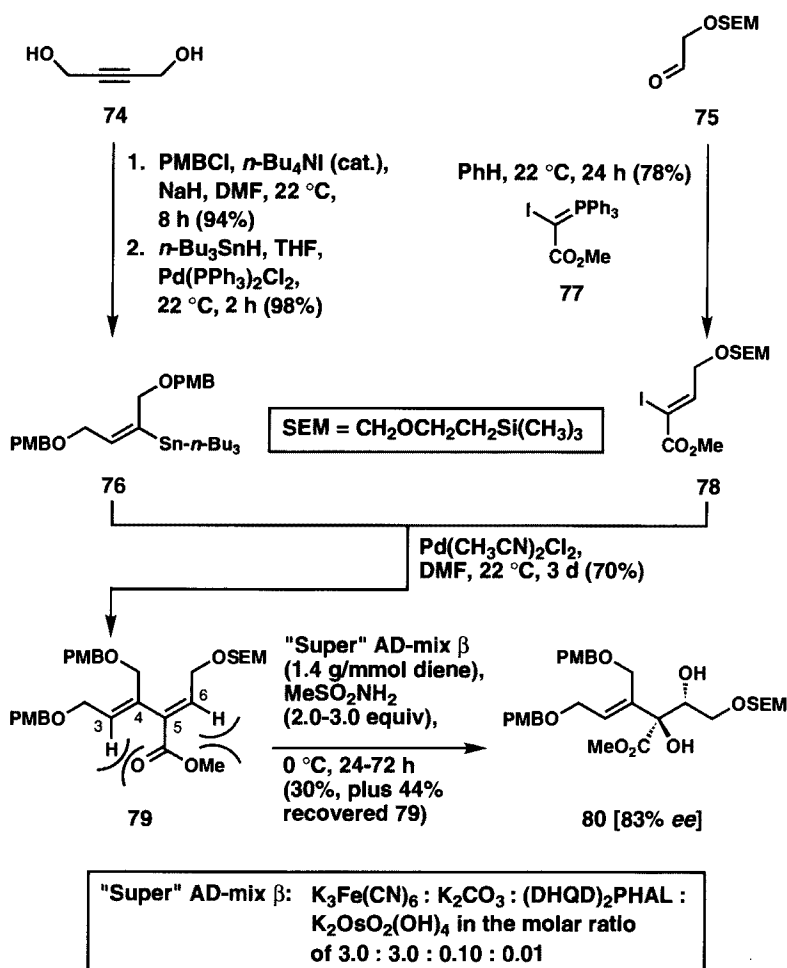
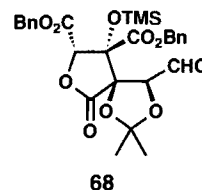
With a triply convergent strategy, the arithmetic demon is defeated and progress on the synthesis can be made on three fronts at once. However, as in many other instances, the natural product is available in sufficient quantity for progress to be made on a fourth front – the final stages of the synthesis. The practice of degrading a natural product to a projected synthetic intermediate and then converting it back to the natural product is known as a *relay* synthesis. It has the distinct practical advantage of providing information about incompatible protecting groups and other transformations before that stage is reached synthetically – a kind of “welcome home” party for precious synthetic material. Degradation and reconstitution studies^{7c,d} on the natural product established that zaragozic acid A (**1**) could be assembled from the triol **73** (Scheme 18), and this was targeted for synthesis. The construction of **73** and its conversion to **1** are discussed below.



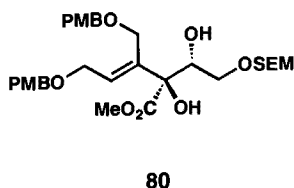
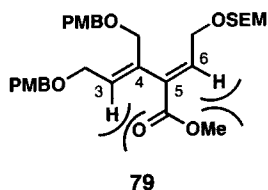
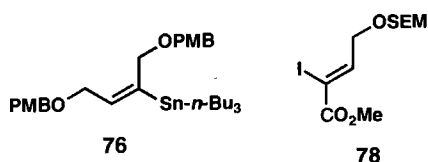
Scheme 18. Synthesis of zaragozic acid A (**1**) from key intermediate **73**.

35.3.2 Synthesis of Key Intermediate Aldehyde **68**

The synthesis of the key intermediate aldehyde **68** is outlined in Schemes 19–21. The two hydroxyls of butyne-1,4-diol (**74**, Scheme 19), a cheap intermediate in the industrial synthesis of THF, can be protected as 4-methoxybenzyl (PMB) ethers in 94 % yield. The triple bond is then *cis*-hydrostannylated with tri-*n*-butyl-tin hydride and a catalytic amount of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ³⁸ to give the vinylstannane **76** in 98 % yield. Note that the stereospecific nature of the *cis*-hydrostannylation absolutely guarantees the correct relative stereochemistry of C-3 and C-4 in the natural product. The other partner for the Stille coupling, vinyl iodide **78**, is prepared by



Scheme 19. Synthesis of aldehyde **68**: the Sharpless AD of diene **79** and synthesis of **80**.



a Wittig reaction between the aldehyde **75** and methyl iodo(triphenylphosphoranylidene) acetate³⁹ (**77**) in 78 % yield. The *Z/E* selectivity exhibited in this Wittig reaction is greater than 30:1; it is instructive to note here that the C5–C6 relative stereorelationship in **68** will stem from the stereochemistry of **78**. The first of the two crucial C–C bond forming reactions (the other is the union of the C-1 side chain with the aldehyde) is the Stille coupling of **76** and **78**. With the standard conditions of $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ catalysis, diene **79** is formed in 75 % yield as a single isomer.

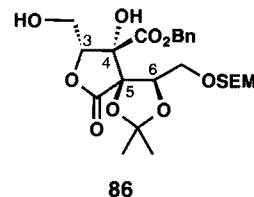
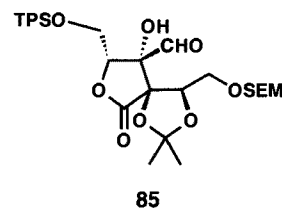
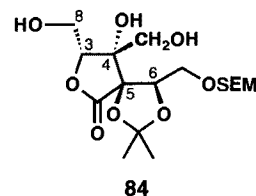
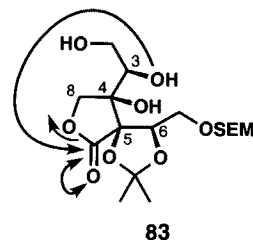
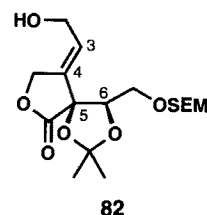
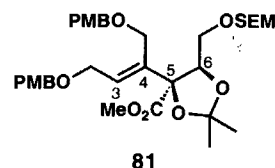
The keynote of the synthesis is the AD of diene **79** to give diol **80** (Scheme 19). In a subsequent paper,^{7d} we reported that a number of combinations of protecting groups were surveyed before the AD worked; optimum results were obtained using diene **79**. When “super” AD-mix β [(DHQD)₂PHAL (10 mol %), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (1 mol %), and methanesulfonamide (3.0 equiv.)] was employed, a modest 30 % yield of diol **80** was obtained, accompanied by unchanged starting material (44 %). There are many possible outcomes of the dihydroxylation: eight possible products may result from the reaction, including tetraols and enantiomers but excluding starting material. It was thus gratifying to find that only two are formed, **80** and its enantiomer (in the approximate ratio of 9.5:1, equivalent to 83 % *ee*). The AD, even on a substrate of this complexity, is still highly regio- and enantioselective! The absolute and relative configurations were established by X-ray crystallographic analysis of later intermediates. The origin of the high regioselectivity of the AD is an interesting issue. At first glance, it would appear that the C3–C4 double bond, not the C5–C6 double bond in **79**, would be the first to react, as it is further away from the ester and therefore more electron-rich. The dihydroxylation is known to favor reaction with electron-rich olefins.⁸ This surprising result was rationalized by considering the probable conformations of the diene calculated by molecular dynamics. These studies show that although the C3–C6 diene system is approximately planar, the ester in **79** is twisted almost into an orthogonal plane, and out of conjugation. Although loss of conjugation between a double bond and an ester by twisting carries a significant energetic penalty (estimated to be about 7.4 kcal mol⁻¹ for methyl acrylate),⁴⁰ the diene **79** can presumably avoid unfavorable allylic strain interactions⁴¹ between the ester and H-3 and H-6 (see **79**, Scheme 19). Also apparent from the modeling studies is that the C–O bond of each of the hydroxymethyl substituents is approximately perpendicular to the plane of the diene, which maximizes hyperconjugative electron withdrawal from each of the double bonds.⁴² The C3–C4 double bond has two of these effects; the C5–C6 double bond only one. It is thus quite likely that the C3–C4 double bond, contrary to superficial expectations, is actually less electron-rich than the C5–C6 double bond, and therefore more resistant to AD.

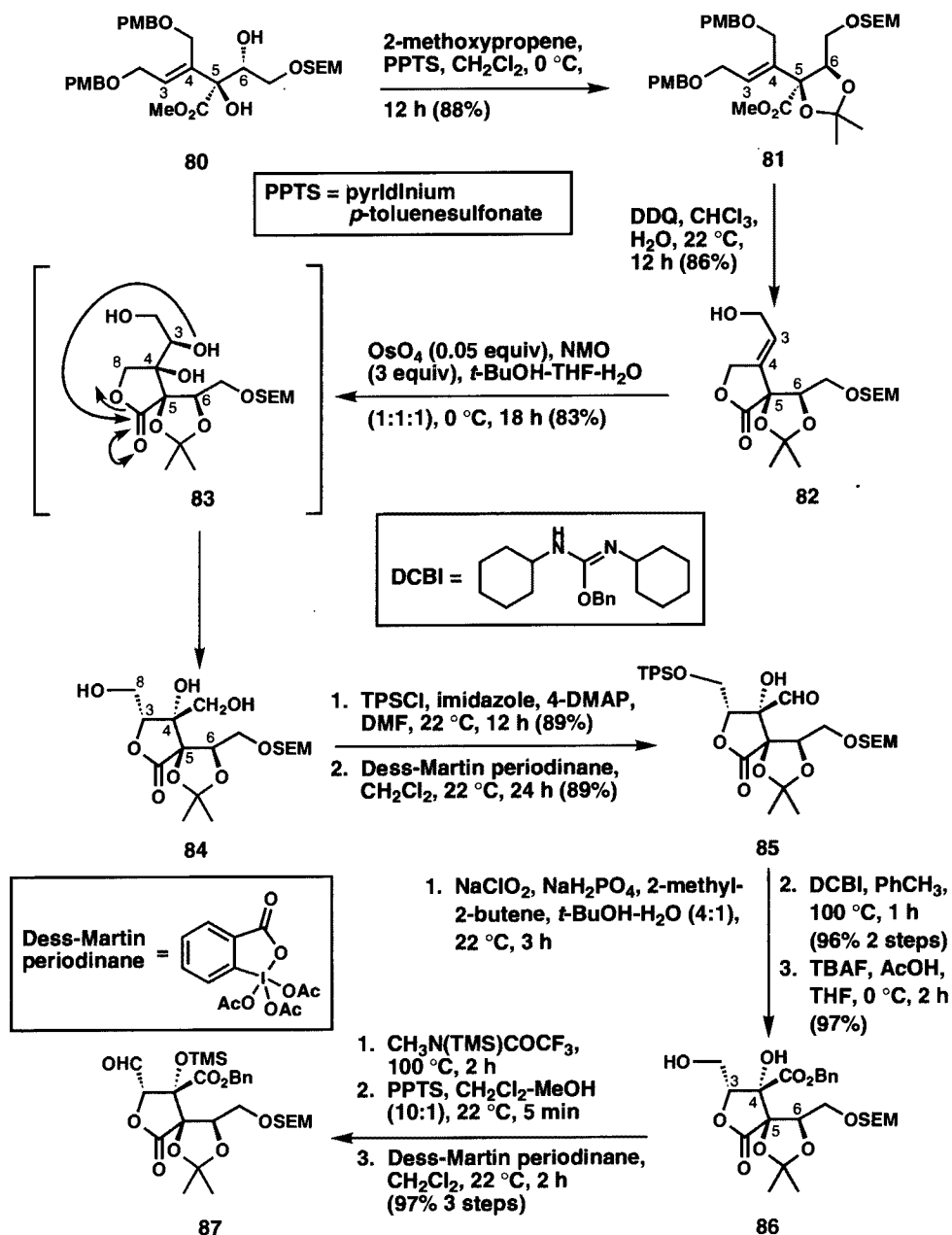
Steric factors also play an important role in determining the regiochemistry of the dihydroxylation, and the modeling studies appear to show that the C3–C4 double bond is more hindered than the C5–C6 double bond, although this is often a rather subjective

judgment. Experimental evidence for the hindered nature of the C3–C4 double bond was obtained when the second dihydroxylation (on **81**, Scheme 20) proved possible only when the PMB groups were first removed. Although the inability to predict which double bond of the diene system would undergo the AD is unsettling, so long as only one double bond reacts selectively the net result of the two dihydroxylations would, in principle, be the same regardless of the order in which they occurred. It was also not possible to predict beforehand, with confidence, which enantiomer of AD-mix to use, because of the complexity of the diene. In principle, however, this last issue is less important, since the other enantiomer could be prepared easily by using the other AD-mix. Having worked out satisfactory conditions for the AD, we are now in a position to address the diastereoselective dihydroxylation.

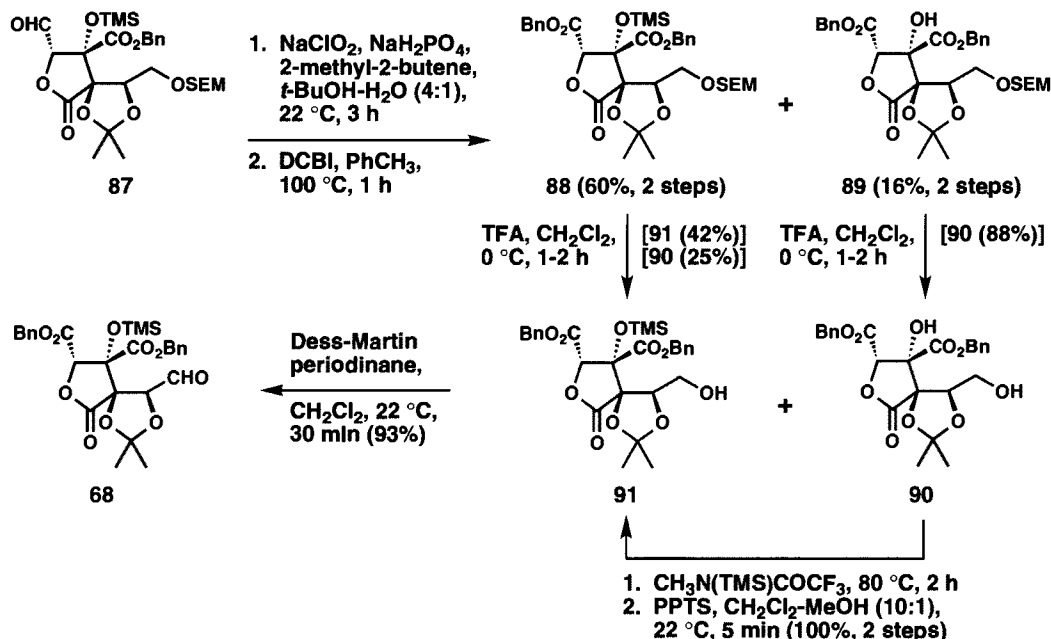
The next key step, the second dihydroxylation, was deferred until the lactone **82** had been formed from compound **80** (Scheme 20). This tactic would alleviate some of the steric hindrance around the C3–C4 double bond, and would create a cyclic molecule which was predicted to have a greater diastereofacial bias. The lactone can be made by first protecting the diol **80** as the acetonide **81** (88% yield), followed by oxidative cleavage of the two PMB groups with DDQ (86% yield).⁴³ Dihydroxylation of **82** with the standard Upjohn conditions¹⁷ furnishes, not unexpectedly, a quantitative yield of the triol **84** as a single diastereoisomer. The triol **84** is presumably fashioned from the initially formed triol **83** by a spontaneous translactonization (see Scheme 20), an event which proved to be a substantial piece of luck, as it simultaneously freed the C-8 hydroxyl from the lactone and protected the C-3 hydroxyl in the alcohol oxidation state.

With the required carbon–oxygen connectivity established, a series of standard functional group and protecting group interchanges eventually gave the aldehyde **68** (see Schemes 20 and 21). Attempts to oxidize simultaneously the C-3 and C-4 hydroxymethyl groups were unsuccessful, affording complex mixtures of lactones and other products. Consequently, the decision was made to protect one of the primary hydroxyls in the form of a silyl ether, and it was found that the less hindered C-8 hydroxyl can be protected as a *tert*-butyldiphenylsilyl (TPS) ether with very high selectivity. Stepwise oxidation of the C-4 hydroxymethyl group (Dess–Martin reagent⁴⁴ and Pinnick oxidation⁴⁵), followed sequentially by esterification with *N,N'*-dicyclohexyl-*O*-benzylisourea (DCBI)⁴⁶ and desilylation with TBAF provides the benzyl ester **86**, via **85**. Unfortunately, repeating the same sequence of oxidations on the C-3 hydroxymethyl group frequently gave poor yields, a result that was attributed to cleavage of the C3–C4 bond by a destructive retro-aldol reaction. Fortunately, however, once the offending C-4 tertiary hydroxyl is protected as a TMS ether [by a convenient bisilylation procedure with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide ($\text{CH}_3\text{N}(\text{TMS})\text{COCF}_3$), followed by monodesilylation], the stepwise oxidation and esterification processes proceed





Scheme 20. Synthesis of aldehyde **68**: the diastereoselective dihydroxylation of **82** and synthesis of **87**.

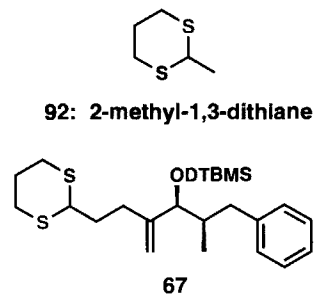


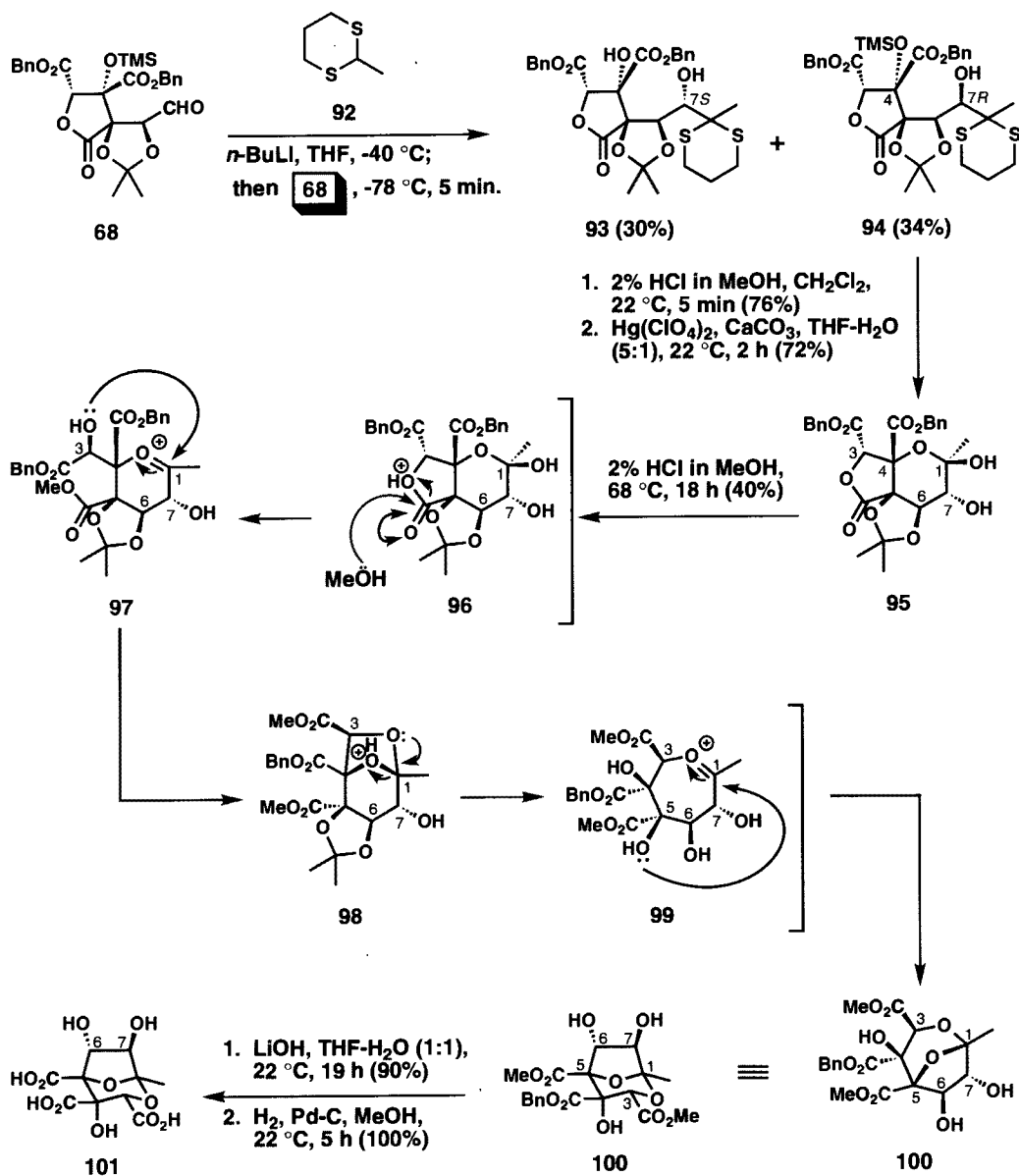
Scheme 21. Synthesis of aldehyde **68**: final oxidations.

smoothly to give a mixture of **88** and **89** via aldehyde **87** (Schemes 20 and 21). The partial desilylation that occurs during the esterification is completed when the SEM protecting group is removed with trifluoroacetic acid in dichloromethane. After a two-step reprotection of the C-4 hydroxyl in the form of a trimethylsilyl ether (see **90** \rightarrow **91**), an efficient Dess–Martin oxidation of the remaining primary alcohol completes the synthesis of key intermediate aldehyde **68**. If the tertiary hydroxyl is left unprotected, an intractable five-membered lactol is formed instead. Although the sequence of oxidations appears circuitous, it is simple to perform, and efficiently gives multigram quantities of the aldehyde **68**.

35.3.3 Model Studies

In total synthesis, model studies are frequently performed on simpler systems prior to the final assault on the target molecule. In the synthesis of zaragozic acid **1**, 2-methyl-1,3-dithiane (**92**) was employed as a simple model for the more elaborate dithiane **67**. Deprotonation of **92** with *n*-butyllithium under standard conditions⁴⁷ and addition of the aldehyde provides a mixture of two diastereoisomers, **93** and **94** (Scheme 22), in approximately equal amounts. One of the diastereoisomers (**93**) lacks the TMS group,





Scheme 22. Synthesis of model compound **101** via a thermodynamically driven rearrangement of **95**.

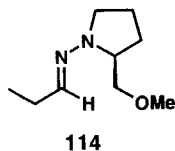
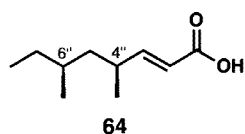
presumably as a result of intramolecular transfer to the C-7 hydroxyl group and subsequent desilylation. The ratio of diastereoisomers was disappointing and could not be improved by changing the reaction conditions. This was the first, and remained the only, time in the synthesis that strict control over diastereoselectivity could not be achieved. It is notable that additions to α -heteroatom-substituted aldehydes are frequently accompanied by high stereoselectivities, although glyceraldehyde type acetonides (as present in **68**) are notorious for undergoing unselective addition reactions. The problem was later partially solved by changing the protecting groups on the aldehyde (**68**),^{7d} but discussion of this work is beyond the scope of this chapter.

The two diastereoisomers (**93** and **94**) can be separated by chromatography and taken forward separately [for clarity, only the sequence for the (7*R*) diastereoisomer is shown in Scheme 22]. Desilylation with 2% HCl–MeOH, followed by removal of the dithiane protecting group with HgClO₄–CaCO₃, affords the lactol **95** in good yield. The dithiane protecting group has a reputation for being rather robust, and several syntheses have failed simply because a dithiane protecting group could not be removed. The ease with which the dithiane in **94** is hydrolyzed in this instance may be attributed to the C-4 hydroxyl group facilitating the hydrolysis of the intermediate thionium ion and the relative entropic benefit of forming an additional ring.

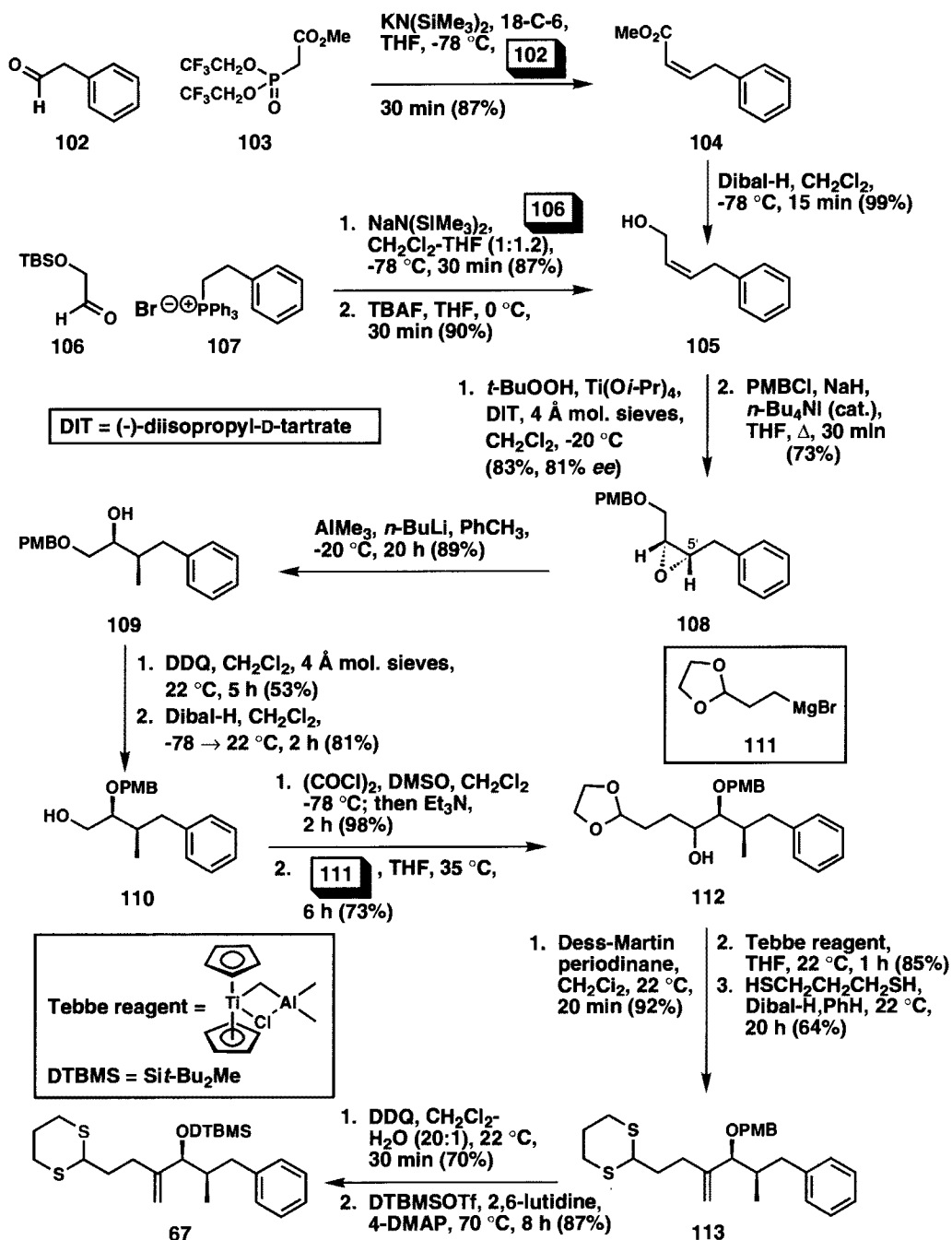
Inspection of lactol **95** reveals that it contains the correctly oxygenated framework of the core of the zaragozic acids. All that is required to complete the core is opening of the three cyclic protecting groups (lactone, lactol, and acetonide) and internal ketalization in the proper sense. Fortunately, refluxing **95** with 2% HCl–MeOH overnight effected all the desired transformations, in some undetermined order, to give the core structure **100** in 40% yield. The only unexpected event was that the less hindered benzyl ester at C-3 had been transesterified by the solvent. During the reaction large numbers of intermediates were observed, but these eventually all converged to **100**, a presumed minimum in the energy surface. The mechanism shown in Scheme 22 is intended only for illustrative purposes; there are likely to be hundreds of nonproductive pathways and possibly many other productive ones in addition to the one shown. However, the mechanism shown is consistent with the isolation of the unprotonated form of **98** when the reaction is incomplete. Furthermore, an intermediate analogous to the seven-membered ring oxonium ion **99** is a likely intermediate in a synthesis of a related molecule.⁴⁸ Comparison of the spectroscopic data of **100** (and of its C-7 epimer) with the data reported for zaragozic acid A provided clear evidence for the constitution of the bicyclic core and the configuration at C-7 of the diastereoisomers **93** and **94**. Finally, the characteristic tricarboxylic acid portion was revealed by stepwise cleavage of the methyl and benzyl esters to give **101** in almost quantitative yield. With the successful demonstration of the ketalization strategy completed, attention is now returned to the synthesis of the natural product.

35.3.4 Synthesis of the Side Chains

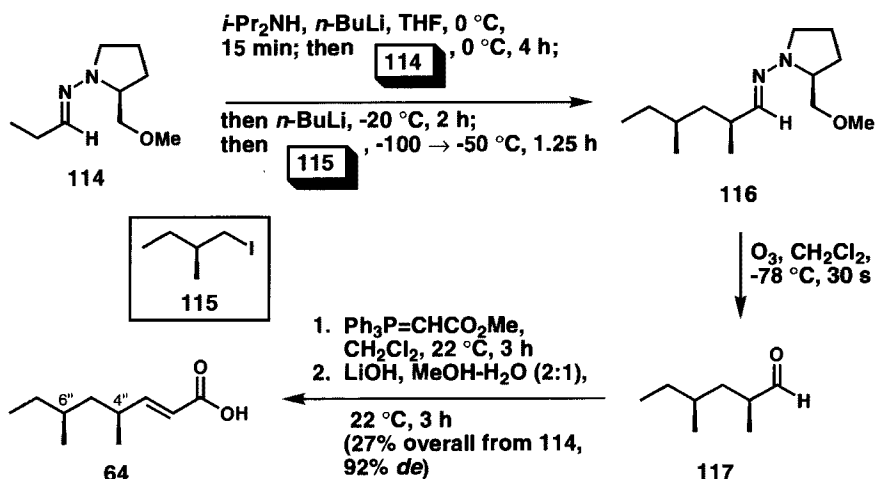
At the time that the work on the AD was being completed, another catalytic asymmetric reaction (the Sharpless AE; see Chapter 19) was being used to prepare the C-1 alkyl side chain. The synthesis is shown in Scheme 23. Allylic alcohol **105** was initially prepared from **102** and **103** by a Still–Gennari phosphonate reaction,⁴⁹ followed by reduction of the methoxycarbonyl group. Later, a more cost-effective sequence to **105** involving a Wittig reaction between **106** and **107**, followed by desilylation was devised. Sharpless epoxidation⁵⁰ of **105** affords, as expected, the corresponding α -epoxide in 83 % yield and 81 % *ee*. Despite some precedent,⁵¹ it was not possible to open the α -epoxide at C-5' with good regioselectivity. As a result, the primary hydroxyl was protected in the form of a PMB ether to furnish **108**. This approach allowed the use of an "ate" complex (AlMe_3 and $n\text{-BuLi}$)⁵² to open the epoxide **108** regioselectively at C-5' (regioselectivity >95:5 by ^1H NMR analysis) giving **109**, and to take advantage of the PMB group in subsequent manipulations. Oxidation of the PMB ether **109** with DDQ in the absence of water⁵³ results in the formation of an unstable acetal which can be immediately reduced with Dibal-H to give the primary alcohol **110** as a single regioisomer. Swern oxidation⁵⁴ of the alcohol **110** then provides the corresponding aldehyde in 98 % yield. When this substance is treated with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide (**111**), acetal **112** is produced as a 1:1 mixture of diastereoisomers in 73 % yield. A series of standard manipulations and a recrystallization (to increase the *ee* to 98 %) then furnishes dithiane **113** as shown in Scheme 23. For a number of reasons that became evident in later stages, it was necessary to replace the PMB group in **113** with the robust di(*tert*-butyl)methylsilyl (DTBMS) protecting group.⁵⁵ Dithiane **67** is in a form suitable for coupling with the aldehyde **68**.



The C-6 acyl side chain **64** can be synthesized very efficiently from the commercially available and enantiomerically pure iodide (*S*)-1-iodo-2-methylbutane (**115**) (Scheme 24). Unfortunately, alkylation with the Evans⁵⁶ and Oppolzer⁵⁷ chiral auxiliaries did not give good control over the C-4'' stereocenter, presumably due to mismatched double diastereoselection. However, alkylation using Enders's hydrazone⁵⁸ **114** and the iodide **115** proceeds with excellent stereocontrol to give, after cleavage of the auxiliary, the aldehyde **117** in 92 % *de*. The aldehyde can then be homologated by a Wittig reaction, after which hydrolysis of the ester provides the requisite acid **64** in 27 % overall yield from **114**.



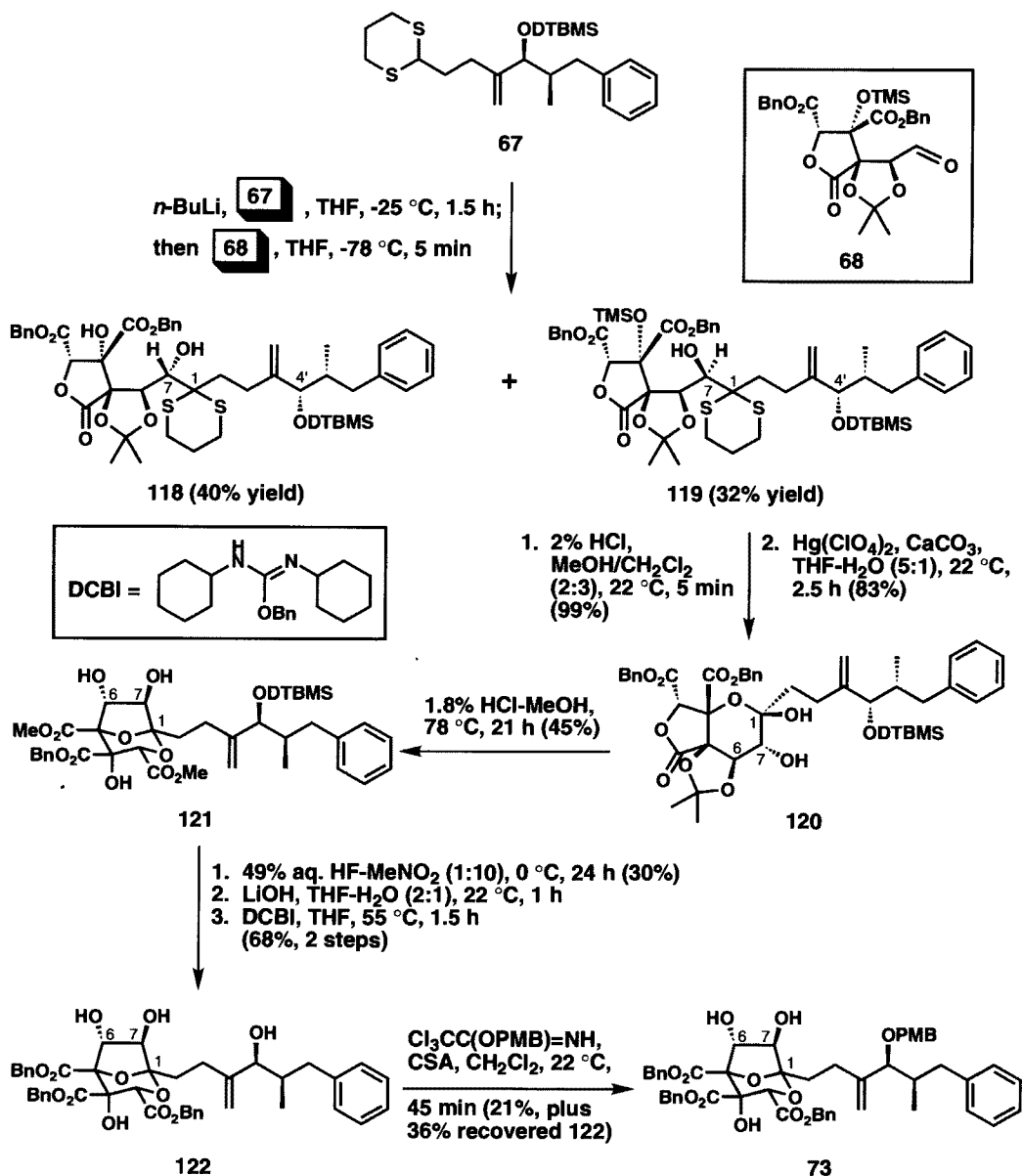
Scheme 23. Synthesis of the C-1 alkyl side chain **67**.



Scheme 24. Synthesis of C-6 acyl side chain **64**.

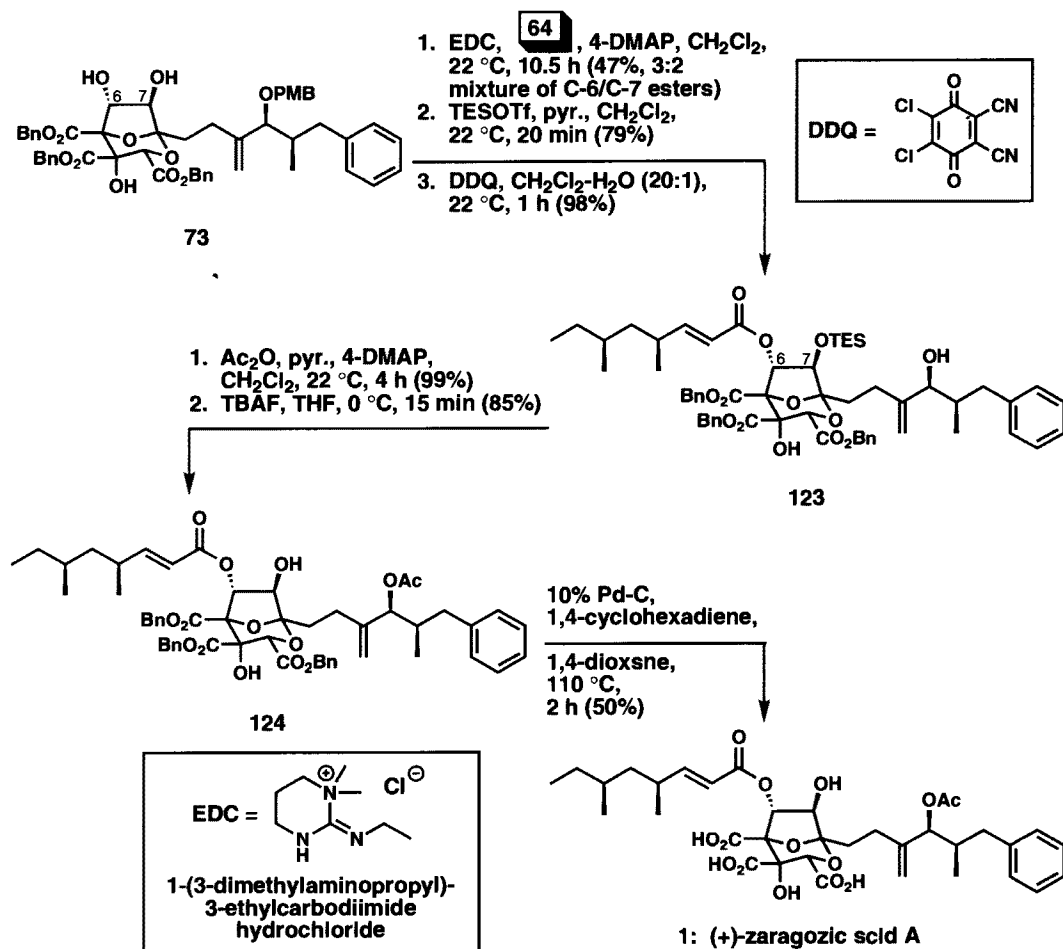
35.3.5 Coupling of Key Intermediates and Completion of the Total Synthesis of Zaragozaic Acid A/Squalestatin S1

The last remaining carbon–carbon bond construction for the synthesis of zaragozic acid A (**1**), the union of **67** and **68**, could now be attempted (see Scheme 25). Using conditions established on the model system (Scheme 22), the dithiane **67** is deprotonated and added to the aldehyde **68** (Scheme 25). As before, a mixture of diastereoisomers, **118** and **119** (**118:119** \approx 40:32), is formed and conditions to improve this could not be found. The desired diastereoisomer **118** can be isolated in pure form by chromatography and desilylated. Hydrolytic cleavage of the dithiane group then gives lactol **120**. Rearrangement occurs on refluxing with 1.8% HCl-MeOH for 16 h to give the zaragozic acid A skeleton **121** in 45% yield. Methanolysis of the C-3 benzyl ester also takes place in this reaction, but this can be easily corrected at a later stage (*vide infra*). The DTBMS group is then removed with 49% aqueous HF in nitromethane (1:10).⁵⁹ This proved to be a difficult transformation and all the other deprotection conditions investigated (e.g. TBAF, TBAF on silica gel, $\text{HF}\cdot\text{pyr.}$, CsF , HF-MeCN , HCl , HF-urea , BF_3 in CH_2Cl_2 ,⁵⁵ $\text{BF}_3\cdot\text{OEt}_2$) either failed to remove the DTBMS group or caused varying degrees of decomposition. The two methyl esters present in **121** (one introduced by nucleophilic opening of the lactone, the other by transesterification of the C-3 benzyl ester) are then hydrolyzed with lithium hydroxide and replaced with benzyl esters using DCBI. This was necessary to avoid concomitant hydrolytic cleavage of the C-6 acyl side chain at the end of the synthesis. The resulting tetraol **122** is then treated

Scheme 25. Synthesis of key intermediate **73**.

with PMB trichloroacetimidate and a small amount of camphorsulfonic acid (CSA) to give predominantly compound **73** in which the allylic hydroxyl is protected as a PMB ether. Other isomers in which the C-6 and C-7 positions are protected can be conveniently separated by flash column chromatography and recycled. Comparison of the spectral data of **73** with a sample obtained by degradation of the natural product indicated that the two samples were indistinguishable.

Introduction of the C-6 acyl side chain proceeded with only modest selectivity in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 4-DMAP, giving a 3:2 mixture of C-6 and C-7 acylated products (Scheme 26).⁶⁰ However,



Scheme 26. Completion of the synthesis of (+)-zaragozic acid A (**1**).

the C-7 acylated product could be readily separated by flash column chromatography, hydrolyzed, and recycled. A TES protecting group is then introduced at the C-7 position and the PMB group on the C-4' hydroxyl is removed by exposure to DDQ to give **123**. Finally, acetylation, desilylation, and transfer hydrogenolysis of the three benzyl esters provides (+)-zaragozic acid A (**1**) via tribenzyl ester **124**.

35.4 Conclusion

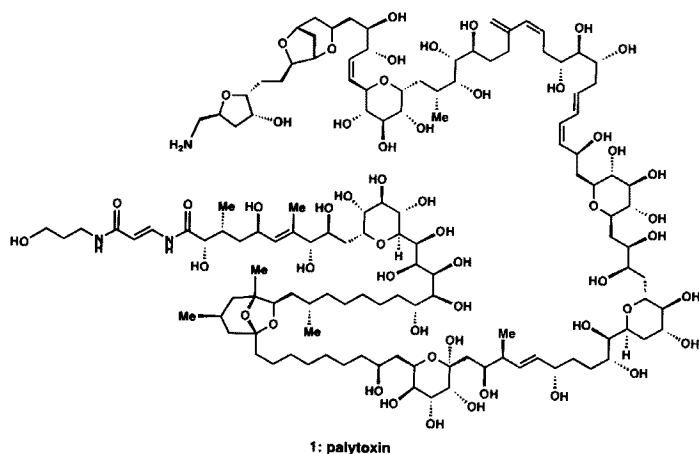
The asymmetric synthesis of zaragozic acid A (**1**) described in this chapter is distinguished by the use of the AD to introduce the first two stereocenters enantioselectively and regioselectively into a complex prochiral diene. A further, completely diastereoselective dihydroxylation established the entire oxygen-carbon connectivity required for the natural product. A series of oxidations then gave the aldehyde **68**. The C-1 side chain of zaragozic acid A, **67**, was then joined to the aldehyde **68**, by a dithiane anion mediated coupling reaction. A multievent, acid-catalyzed rearrangement then produced the basic bicyclic core structure **121**, which was finally converted into the natural product by a series of standard reactions. The described synthesis was soon to be joined by three others, one^{61d} of zaragozic acid A (**1**) and two^{61a-c} of the simpler zaragozic acid C (**43**).^{62,63}

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63. The substantial contributions of Alan Nadin and Eddy Yue to the preparation of this chapter are gratefully acknowledged.



Y. Kishi (1994)

Palytoxin

36.1 Introduction

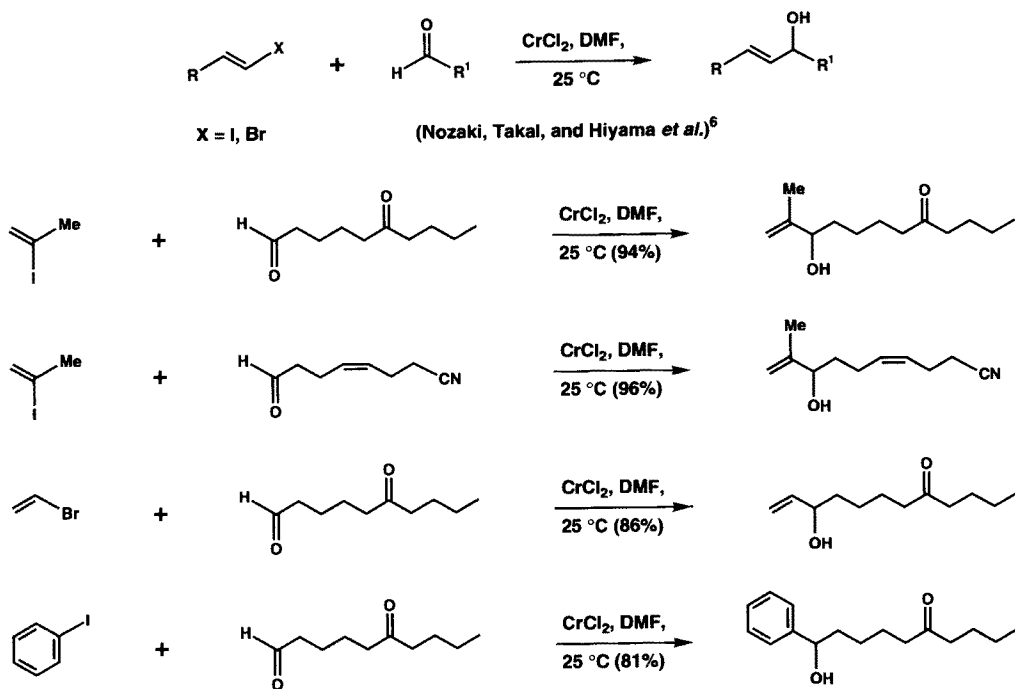
Palytoxin (**1**)¹ has been claimed to be the most poisonous non-peptidic substance currently known to man, although this distinction may now belong to maitotoxin,² a more complex and even larger marine natural product. Isolated from certain soft corals of the genus *Palythoa*, palytoxin provided formidable challenges to both structure elucidation and synthetic chemists alike. Indeed, it was not until 1981, and after long campaigns, that the gross structure of palytoxin was simultaneously and independently reported by two groups. The Hirata group from Japan reported their work in *Tetrahedron Letters*,³ while the Moore team in Hawaii disclosed their results in the *Journal of the American Chemical Society*.⁴

Kishi and his coworkers completed the total synthesis of palytoxin in 1994. Before this feat could be achieved, however, it was necessary to unambiguously establish the relative and absolute stereochemical relationships within the reported gross structure. Through the use of a combination of degradation, synthetic, and spectroscopic techniques, a single isomer among the 2⁷¹ stereoisomers allowed by the 71 stereochemical elements (64 stereogenic and 7 geometrical) of the palytoxin structure was defined. The constitution and absolute stereochemistry of the palytoxin molecule is thus as shown in **1**. In this chapter, we outline the monumental endeavor that culminated in the completion of the total synthesis of palytoxin by the Kishi group in 1994.⁵ This landmark achievement

was accompanied by the discovery and development of a number of important reactions. Among these, the most important ones are: (a) the development of the $\text{NiCl}_2/\text{CrCl}_2$ -catalyzed coupling reaction between vinyl iodides and aldehydes originally discovered by the Nozaki group; (b) the $\text{Pd}(0)$ -catalyzed and thallium hydroxide (TlOH) assisted synthesis of *cis-trans* conjugated dienes from vinyl iodides and vinyl boronic acids; and (c) new methods for the construction of *N*-acyl vinylogous ureas. Before proceeding with the retrosynthetic analysis and total synthesis of palytoxin, it would be instructive to describe the $\text{NiCl}_2/\text{CrCl}_2$ -catalyzed coupling of vinyl iodides and aldehydes in some detail.

36.1.1 The $\text{NiCl}_2/\text{CrCl}_2$ -Mediated Coupling Reaction

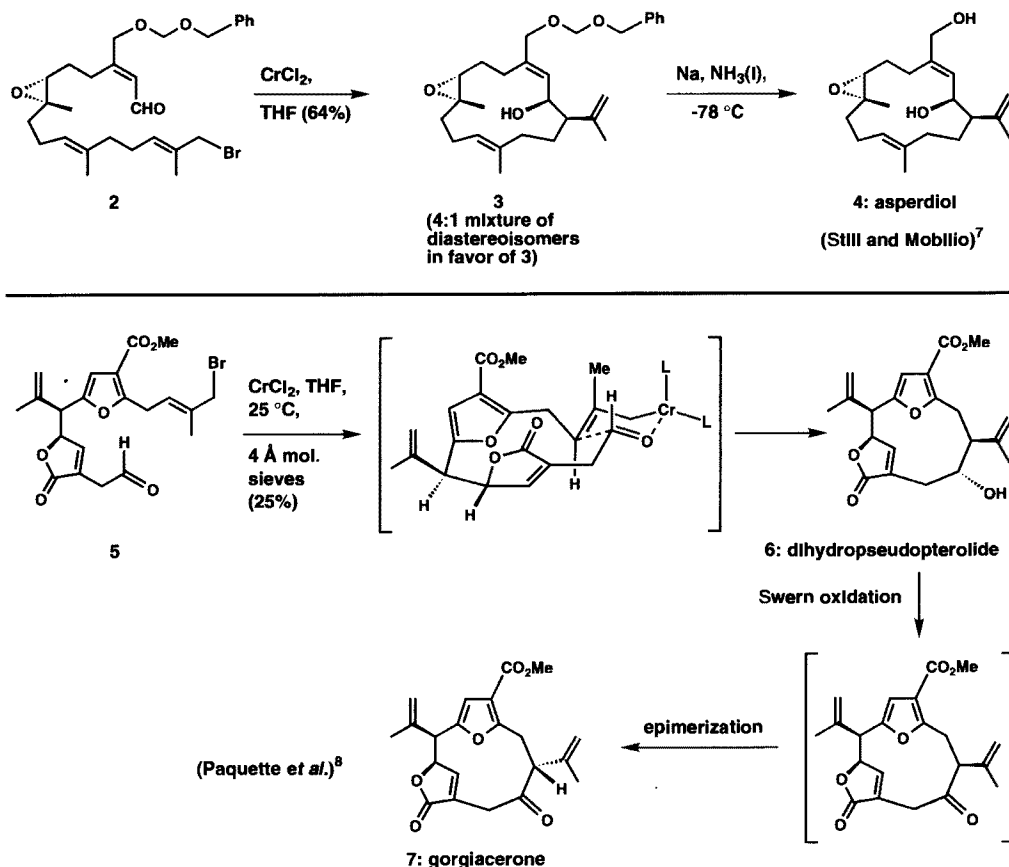
In 1983, Nozaki, Takai, Hiyama, and their coworkers disclosed that vinyl and aryl iodides or bromides are reduced with chromium(II) chloride, and that the resulting organochromium(III) species react smoothly with a host of aldehydes to give allylic or benzylic alcohols in excellent yields.⁶ As shown in Scheme 1, the chromium(II) chloride-mediated carbonyl addition can be conducted efficiently at



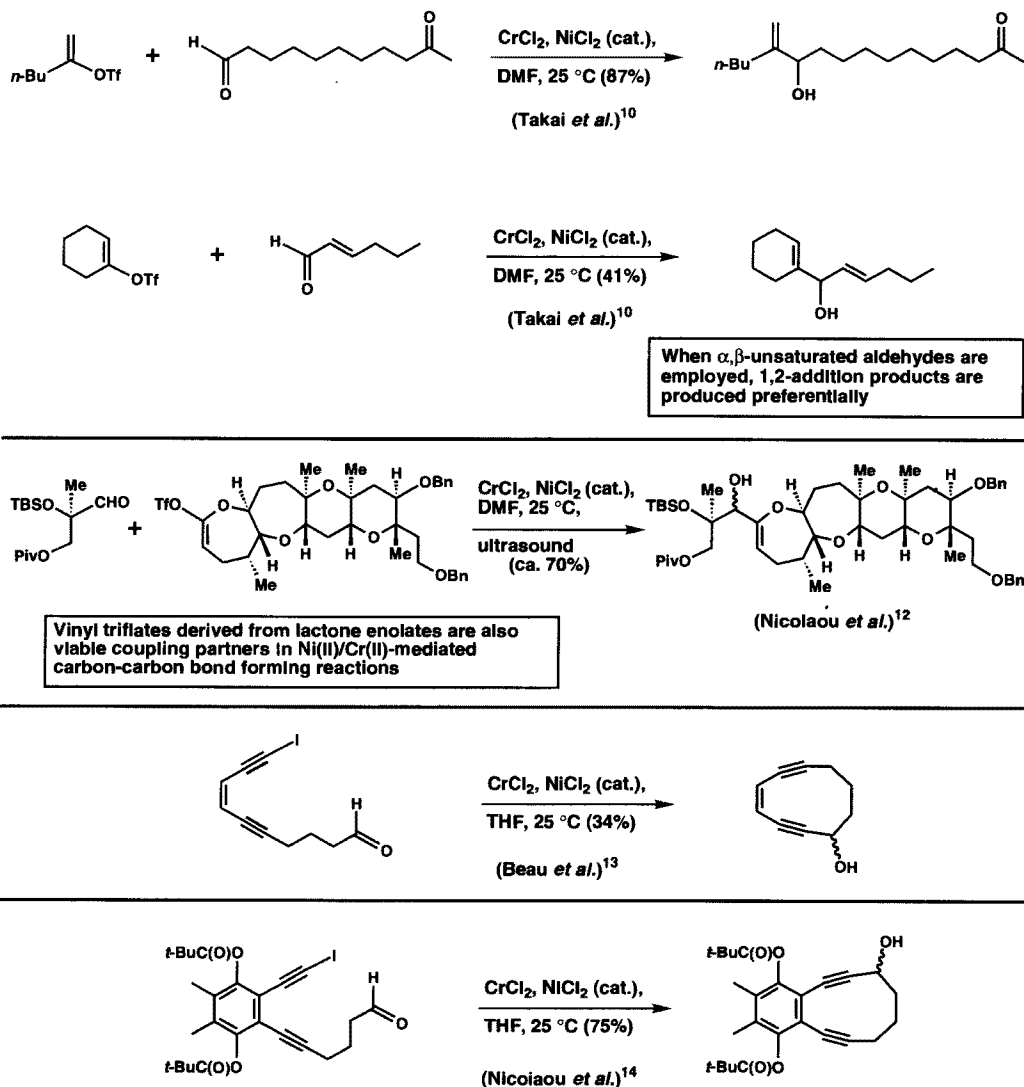
Scheme 1. The chromium(II) chloride-mediated carbonyl addition process of Nozaki, Takai, and Hiyama.

room temperature in the dipolar aprotic solvent dimethylformamide (DMF). It is very significant that this carbon–carbon bond forming reaction is highly chemoselective; aldehyde carbonyls are attacked selectively, even in the presence of other electrophilic functional groups such as ketones, esters, and nitriles. The ability of organochromium(III) reagents to discriminate between inherently electrophilic functional groups is an asset that bodes well for uses in multifunctional contexts.

Allylic bromides can also serve as progenitors for nucleophilic organochromium reagents. An elegant example is found in Still and Mobilio's synthesis of the 14-membered cembranoid asperdiol (**4**) (see Scheme 2).⁷ In the key step, reduction of the carbon–bromine bond in **2** with chromium(II) chloride in THF is attended by intramolecular carbonyl addition, affording a 4:1 mixture of cembranoid diastereoisomers in favor of the desired isomer **3**. Reductive cleav-



Scheme 2. Use of allylic bromides in CrCl_2 -mediated bond formations.

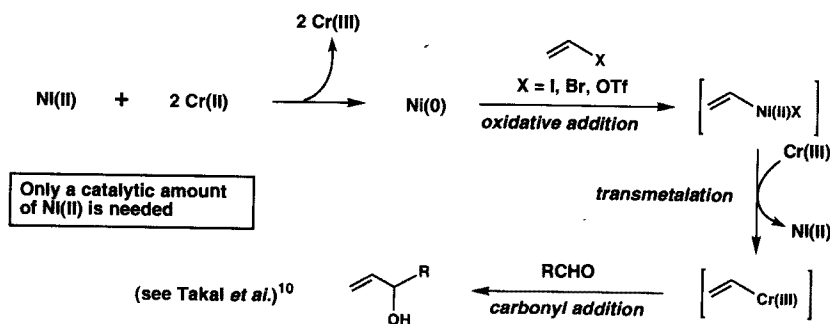


Scheme 3. Examples of Ni(II)/Cr(II)-mediated bond forming reactions.

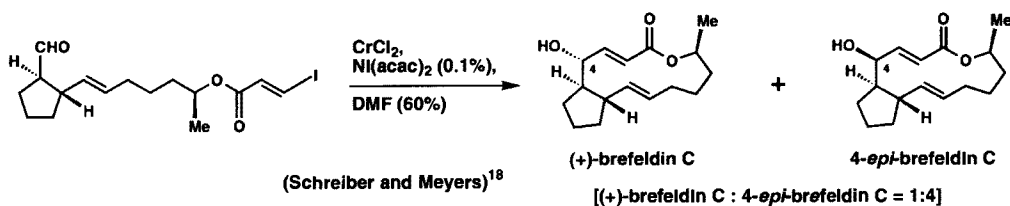
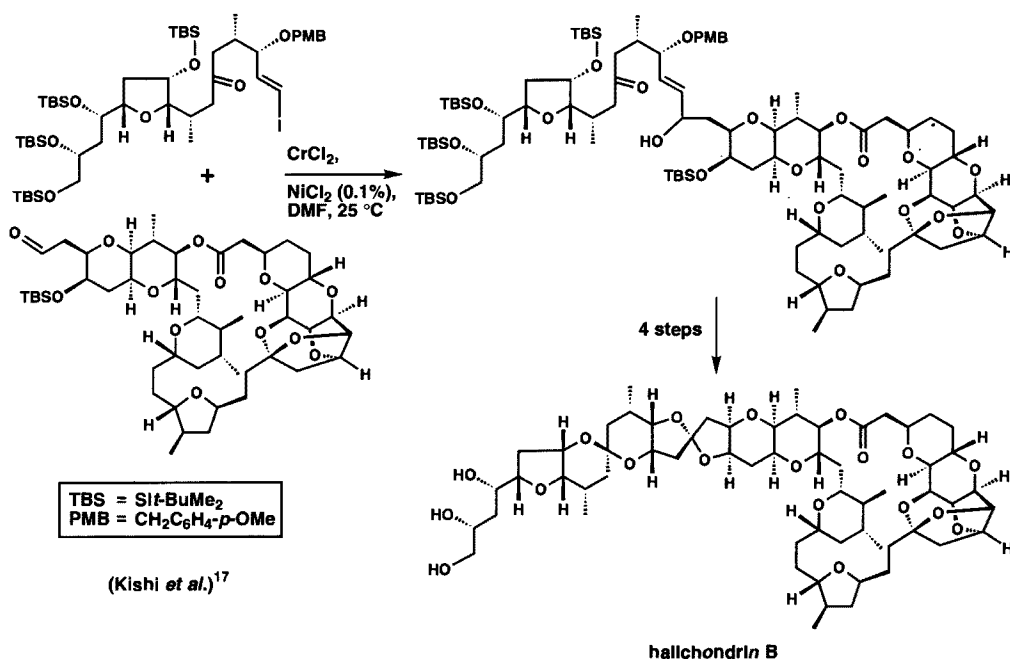
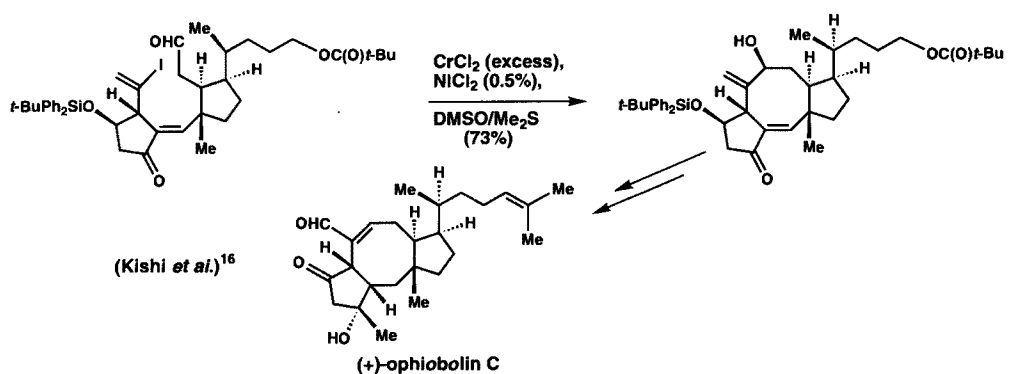
age of the benzyloxymethyl ether in **3** unveils asperdiol (**4**). In more recent studies, Paquette *et al.* disclosed the remarkable chromium(II) chloride mediated cyclization of **5**, the pivotal step in stereocontrolled total syntheses of dihydropseudopterolide (**6**) and gorgiacerone (**7**)⁸ (see Scheme 2).

Following the pioneering 1983 report of Nozaki *et al.*,⁵ Kishi and coworkers used the chromium(II) chloride mediated coupling of vinyl iodides and aldehydes, and soon discovered that the outcome of this type of coupling reaction mysteriously depended on the source and batch of the chromium(II) chloride used. Suspecting a crucial role of an unknown impurity in certain batches of chromium(II) chloride, the Kishi group systematically examined the effect of transition metal salts on the reaction and found that nickel(II) chloride has a dramatic and beneficial effect.⁹ In the meantime, the Takai group had been doing some exploratory work of their own, and independently arrived at the same discovery at about the same time.¹⁰ In recent years, the NiCl₂/CrCl₂-mediated carbon-carbon bond forming reaction has enjoyed widespread use for the coupling of vinyl iodides and other related substrates with aldehydes.¹¹ Indeed, in addition to vinyl iodides (and bromides), vinyl triflates (also known as enol triflates) and acetylenic iodides are also viable precursors for nucleophilic organochromium(III) reagents (for examples, see Scheme 3).^{10,12-14} Vinyl triflates are conveniently formed by the trapping of enolate oxygens with reactive triflating agents, such as *N*-phenyltrifluoromethanesulfonimide, and are particularly attractive as substrates in this Ni(II)/Cr(II)-mediated coupling process because several methods are available for their regioselective generation.¹⁵ Acetylenic iodides are also capable of participating in this type of coupling reaction as exemplified by the intramolecular examples shown in Scheme 3.

The Ni(II)/Cr(II)-mediated coupling reaction employs an excess of chromium(II) chloride and a catalytic amount of nickel(II) chloride (0.1 %). The preferred solvent for this reaction is usually DMF, although THF, DMF/THF, or DMF/Me₂S may also be used. The ability to activate the vinyl iodide (or related) substrate at ambient



Scheme 4. Presumed mechanism for the Ni(II)/Cr(II)-mediated coupling reaction.



Scheme 5. Applications of the Ni(II)/Cr(II)-mediated coupling reaction to total synthesis.

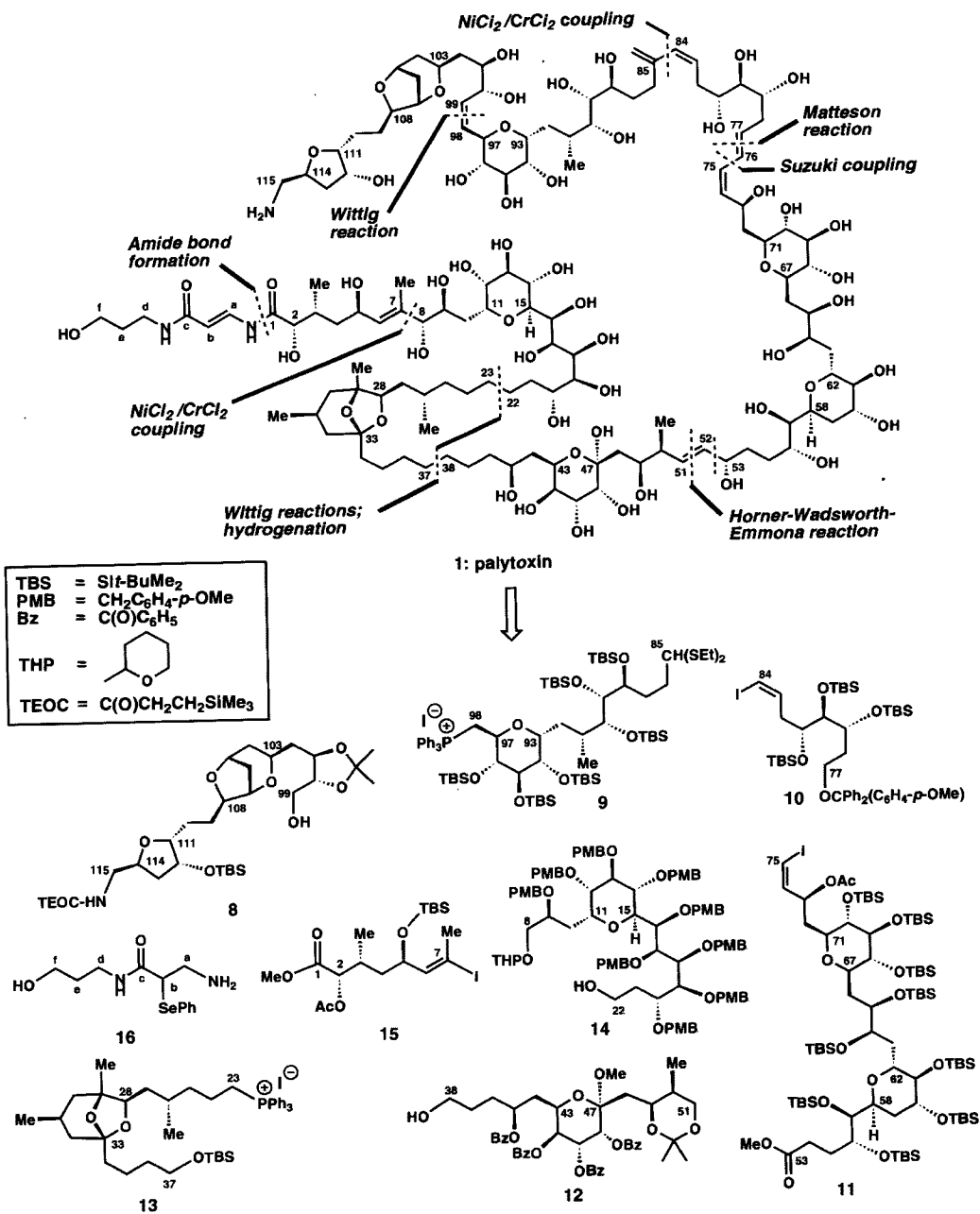
temperature and in the presence of the aldehyde coupling partner offers an attractive advantage over conventional carbonyl addition processes that use organometallic reagents such as Grignard reagents, organolithium reagents, or organocuprates. It is important to note that molecular oxygen is detrimental to the Ni(II)/Cr(II)-mediated coupling reaction and should be rigorously excluded.

A plausible mechanism accounting for the catalytic role of nickel(II) chloride has been advanced (see Scheme 4).¹⁰ The process may be initiated by reduction of nickel(II) chloride to nickel(0) by two equivalents of chromium(II) chloride, followed by oxidative addition of the vinyl iodide (or related substrate) to give a vinyl nickel(II) reagent. The latter species may then undergo transmetalation with a chromium(III) salt leading to a vinyl chromium(III) reagent which then reacts with the aldehyde. The nickel(II) produced in the oxidative addition step reenters the catalytic cycle.

Numerous applications of the Ni(II)/Cr(II)-mediated coupling reaction in total synthesis have already been reported.¹¹ Some of the more noteworthy examples derive from Kishi's laboratories and played a role in the syntheses of such complex molecules as (+)-ophiobolin C¹⁶ and halichondrin B¹⁷ (see Scheme 5). Another elegant application can be found in the enantioselective total syntheses of (+)-brefeldin C and 4-*epi*-brefeldin C by Schreiber and Meyers (see Scheme 5).¹⁸

36.2 Retrosynthetic Analysis and Strategy

The palytoxin molecule (see **1**) possesses a richly functionalized and substituted 115 carbon atom chain. In palytoxin, one finds ten rings, each containing one oxygen atom, seven carbon-carbon double bonds, and an *N*-acyl vinylogous urea. Owing to the size and complexity of the molecule, a convergent approach is required. With a view toward maximizing convergency, the palytoxin structure can be retrosynthetically disassembled as shown in Scheme 6. Disconnection of the strategic bonds indicated on structure **1** by the retroversions of the reactions shown at each position, reveals key intermediates **8–16** as potential building blocks. In the synthetic direction, the plan will entail construction of the C1–C115 skeleton [palytoxin carboxylic acid (**32**)], followed by attachment of the unusual *N*-acyl vinylogous urea moiety. Palytoxin carboxylic acid (**32**) was projected to be formed by a ketophosphonate-aldehyde coupling reaction (a Horner-Wadsworth-Emmons reaction) joining intermediates **24** and **30**, followed by reduction of the C-53 carbonyl group and complete deprotection. The requisite fragments, aldehyde **24** (C1–C51) and ketophosphonate **30** (C52–C115) are to be constructed through the union and elaboration of intermediates C1–C7 (**15**), C8–C22 (**14**), C23–C37 (**13**) and C53–C75 (**11**), C76 (LiCH[B(OCH₂CH₂CH₂O)]₂), C77–C84 (**10**), C85–C98 (**9**), C99–C115 (**8**), respectively. The overall



Scheme 6. Retrosynthetic analysis of palytoxin (**1**).

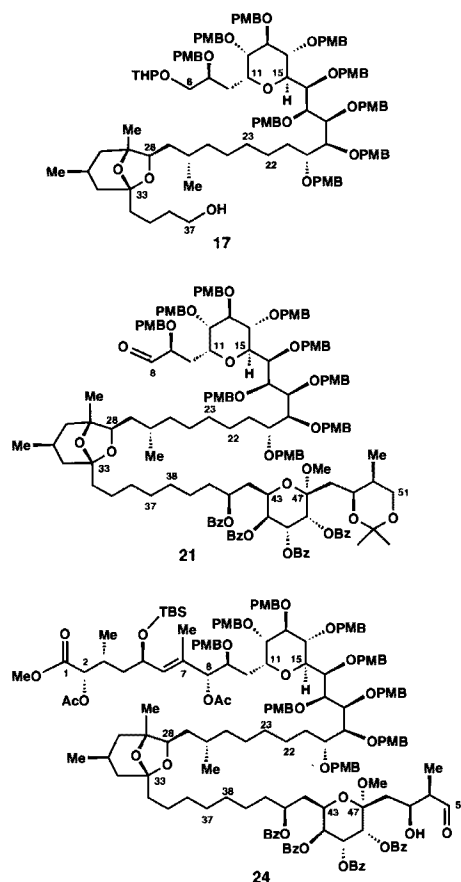
strategy requires a prudent choice of suitable protecting groups and formation of the indicated strategic bonds in the following order: (a) for segment C1–C51: C22–C23 (Wittig reaction followed by hydrogenation), C37–C38 (Wittig reaction followed by hydrogenation), and C7–C8 (NiCl₂/CrCl₂-mediated coupling); (b) for segment C52–C115: C98–C99 (Wittig reaction), C84–C85 (NiCl₂/CrCl₂-mediated coupling), C76–C77 (Matteson reaction)²² and C75–C76 (palladium(0)-catalyzed Suzuki coupling)²⁰; (c) C51–C52 (keto-phosphonate–aldehyde coupling); and (d) C1–N (amide bond formation).

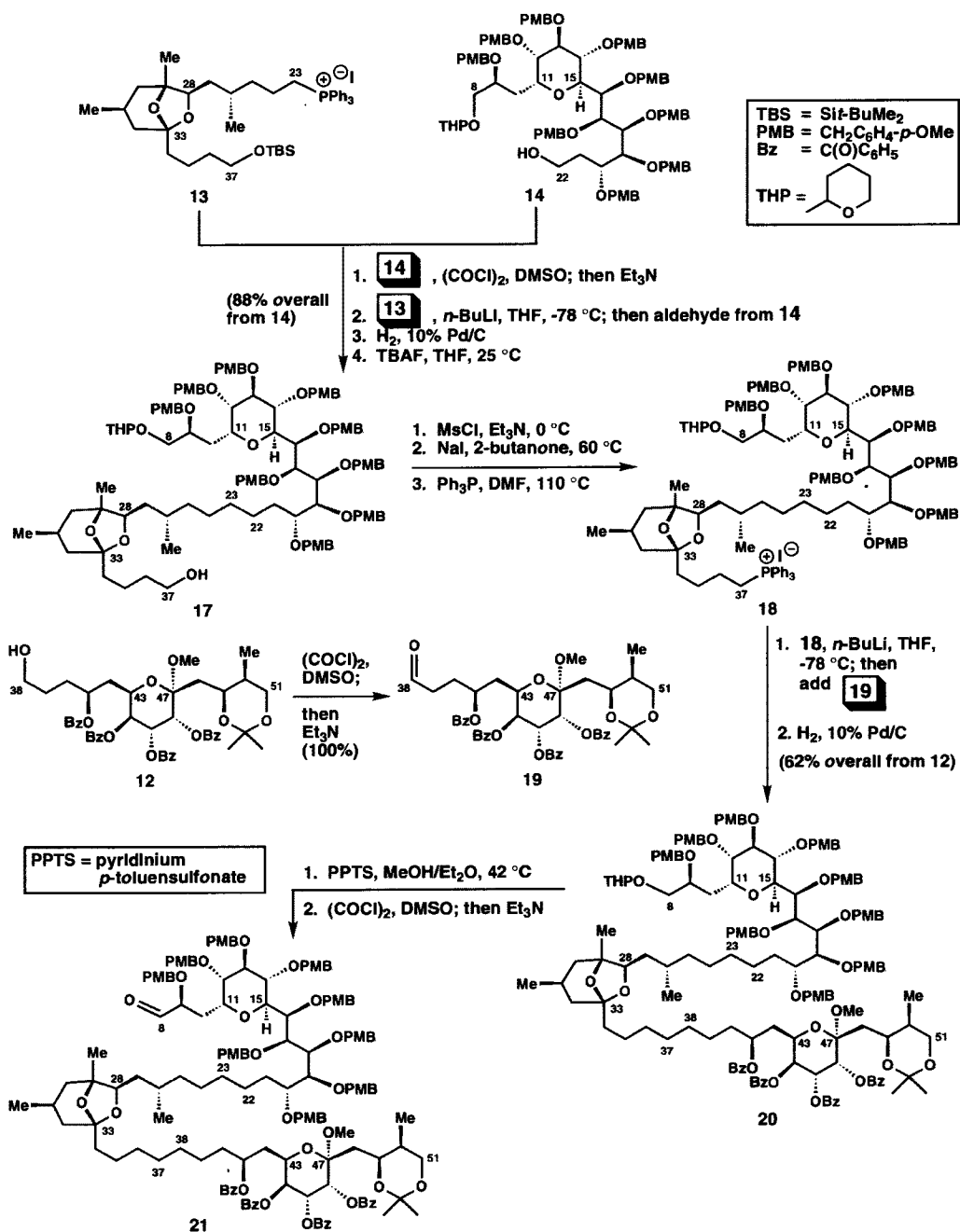
The execution of this brilliant strategy, culminating in the total synthesis of palytoxin (**1**) is described below.

36.3 Total Synthesis

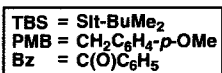
Our journey to palytoxin (**1**) begins with the enantiomerically pure building blocks **8–15** shown in Scheme 6. We will first address the construction of the requisite aldehyde fragment **24** (see Scheme 7). The aldehyde, which is generated from the primary alcohol **14** by Swern oxidation, reacts smoothly with the phosphorus ylid formed by treatment of phosphonium salt **13** in THF with *n*-butyllithium at -78°C , affording a mixture of *cis* and *trans* alkenes (88% yield from **14**). Catalytic hydrogenation of the newly formed C22–C23 double bond, followed by fluoride-induced desilylation of this product leads to compound **17** in 88% overall yield from **14**. The C-37 primary hydroxyl in **17** is then converted by standard chemistry (mesylation, iodide displacement, and reaction with triphenylphosphine) to phosphonium salt **18** in high yield. Reaction of the phosphorus ylid generated from **18** and *n*-butyllithium in THF with aldehyde **19**, formed in quantitative yield by Swern oxidation of alcohol **12**, followed by hydrogenation of the resulting double bond, provides the desired fragment **20** in 62% overall yield from **12**. Selective removal of the tetrahydropyranyl (THP) group from **20** by exposure to methanolic pyridinium *p*-toluenesulfonate (PPTS) at 42°C , followed by Swern oxidation of the resulting alcohol, affords aldehyde **21**.

The NiCl₂/CrCl₂-mediated coupling of the iodoolefin **15** with aldehyde **21** proceeds smoothly to afford, in 64% yield, the desired allylic alcohol **22** together with a diastereomeric substance (18%), epimeric at C-8. The latter compound can be converted to the desired isomer **22** by way of an oxidation/reduction sequence (91% overall yield and 8:1 stereoselectivity). Acetylation of **22**, followed by removal of the acetonide protecting group with PPTS in methanol–ether at 40°C , results in the formation of the diol **23** (97% overall yield). Finally, selective oxidation of the C-51 primary alcohol in compound **23** with RuCl₂(PPh₃)₃¹⁹ leads to the targeted C1–C51 aldehyde fragment **24** (72–81% yield, Scheme 7).

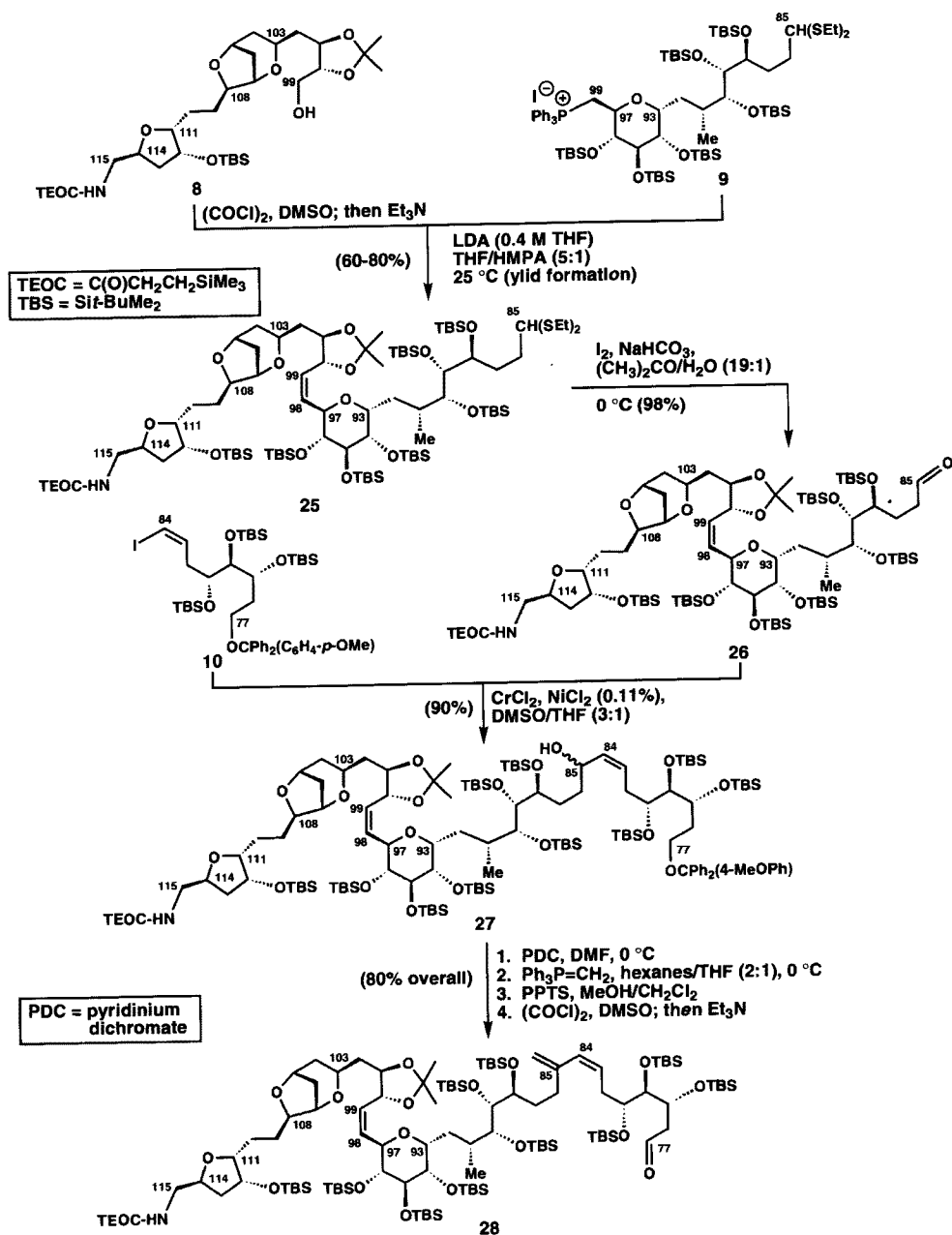




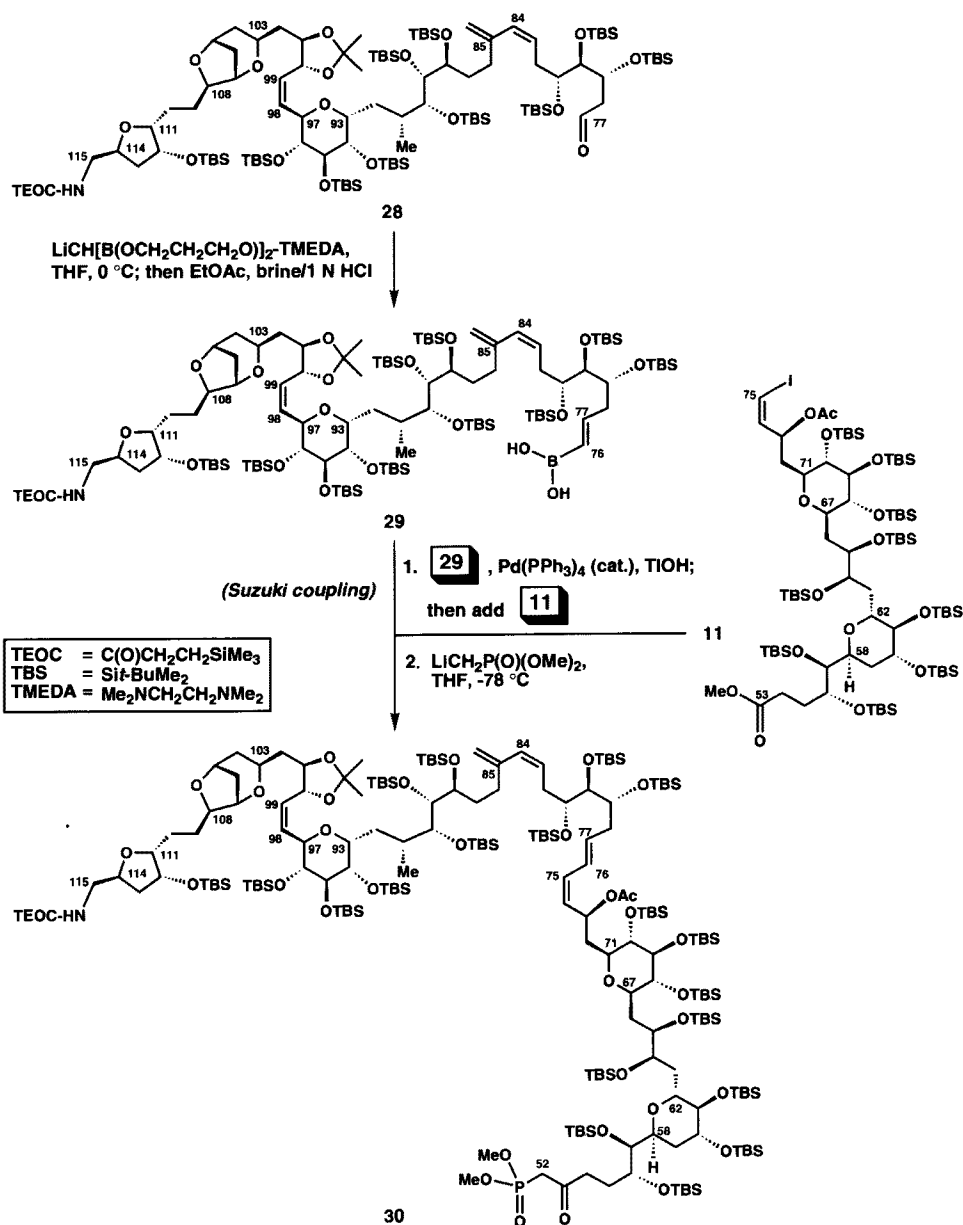
Scheme 7. Construction of C1–C51 aldehyde **24**: synthesis of intermediate **21**.



Scheme 7. Synthesis of C1–C51 aldehyde **24**: final stages.



Scheme 8. Construction of C52–C115 ketophosphonate **30**: synthesis of intermediate **28**.

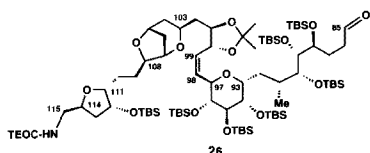


Scheme 8. Synthesis of C52–C115 ketophosphonate **30**; final stages.

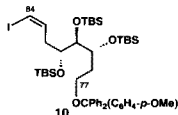
The synthesis of the C52–C115 ketophosphonate fragment **30** (see Scheme 8) commences with the union of the aldehyde derived from alcohol **8** by Swern oxidation with the ylid generated from phosphonium salt **9** and lithium diisopropylamide (LDA) in THF/HMPA at 25 °C to yield the *cis* olefin **25** in 60–80 % yield from **8**. It is important to note at this juncture that these coupling conditions were identified only after systematic study, and are necessary in order to avoid epimerization at C-97. This initially observed epimerization proceeds by a process involving ring opening and closing adjacent to the ylid site (tetrahydropyran system C93–C97). The *cis*–*trans* stereoselectivity of this Wittig coupling reaction is $\geq 8:1$ in favor of the desired *cis* double bond.

The aldehyde function at C-85 in **25** is unmasked by oxidative hydrolysis of the thioacetal group (I_2 , NaHCO_3) (98 % yield), and the resulting aldehyde **26** is coupled to *Z*-iodoolefin **10** by a $\text{NiCl}_2/\text{CrCl}_2$ -mediated process to afford a *ca.* 3:2 mixture of diastereoisomeric allylic alcohols **27**, epimeric at C-85 (90 % yield). The low stereoselectivity of this coupling reaction is, of course, inconsequential, since the next operation involves oxidation [pyridinium dichromate (PDC)] to the corresponding enone and olefination with methylene triphenylphosphorane to furnish the desired diene system (70–75 % overall yield from dithioacetal **9**). Deprotection of the C-77 primary hydroxyl group by mild acid hydrolysis (PPTS, $\text{MeOH}-\text{CH}_2\text{Cl}_2$), followed by Swern oxidation, then leads to the C77–C115 aldehyde **28** in excellent overall yield.

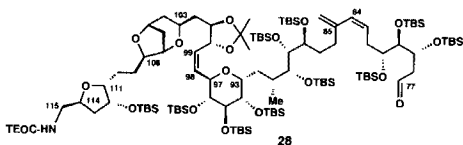
The next task in the synthesis is the coupling of intermediates **28** and **11** and construction of the C74–C77 *cis*–*trans* diene system of palytoxin. To this end, the Kishi group focused on a palladium-catalyzed C–C bond forming reaction – the Suzuki coupling of a boronic acid and an iodoolefin.²⁰ Early experiments based on the addition of catecholborane to a terminal alkyne to form the required boronic acid under the usual reaction conditions were discouraging. In the face of these initial failures, the Harvard researchers proceeded to develop alternative and improved procedures for the Suzuki coupling process. First, they observed the beneficial effect of thallium hydroxide (TlOH) on the coupling process,²¹ and, second, they utilized Matteson's reagent,²² $\text{LiCH}[\text{B}(\text{OCH}_2\text{CH}_2\text{CH}_2\text{O})_2]$, to prepare the requisite vinylboronic acid. Thus, reaction of aldehyde **28** with $\text{LiCH}[\text{B}(\text{OCH}_2\text{CH}_2\text{CH}_2\text{O})_2]$, followed by acid workup, yields the desired *trans*-vinylboronic acid **29** with 8:1 to 10:1 stereoselectivity. The mixture of vinylboronic acids **29** is then allowed to react with the (*Z*)-iodoolefin **11** in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ and TlOH to yield the desired $\Delta^{74,75}$ -*cis*/ $\Delta^{76,77}$ -*trans* diene in 70 % overall yield from the alcohol precursor of aldehyde **28**. Despite the stereoisomeric mixture of boronic acids used, the isolated diene, at this stage, was found to be isomerically pure and could be converted to the targeted ketophosphonate **30**, in essentially quantitative yield, by exposure to the lithio derivative of dimethyl methylphosphonate [$\text{MeP}(\text{O})(\text{OMe})_2$]. It is worth mentioning here that C-76 and C-52 of palytoxin are intro-



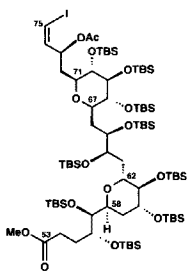
26



10



28



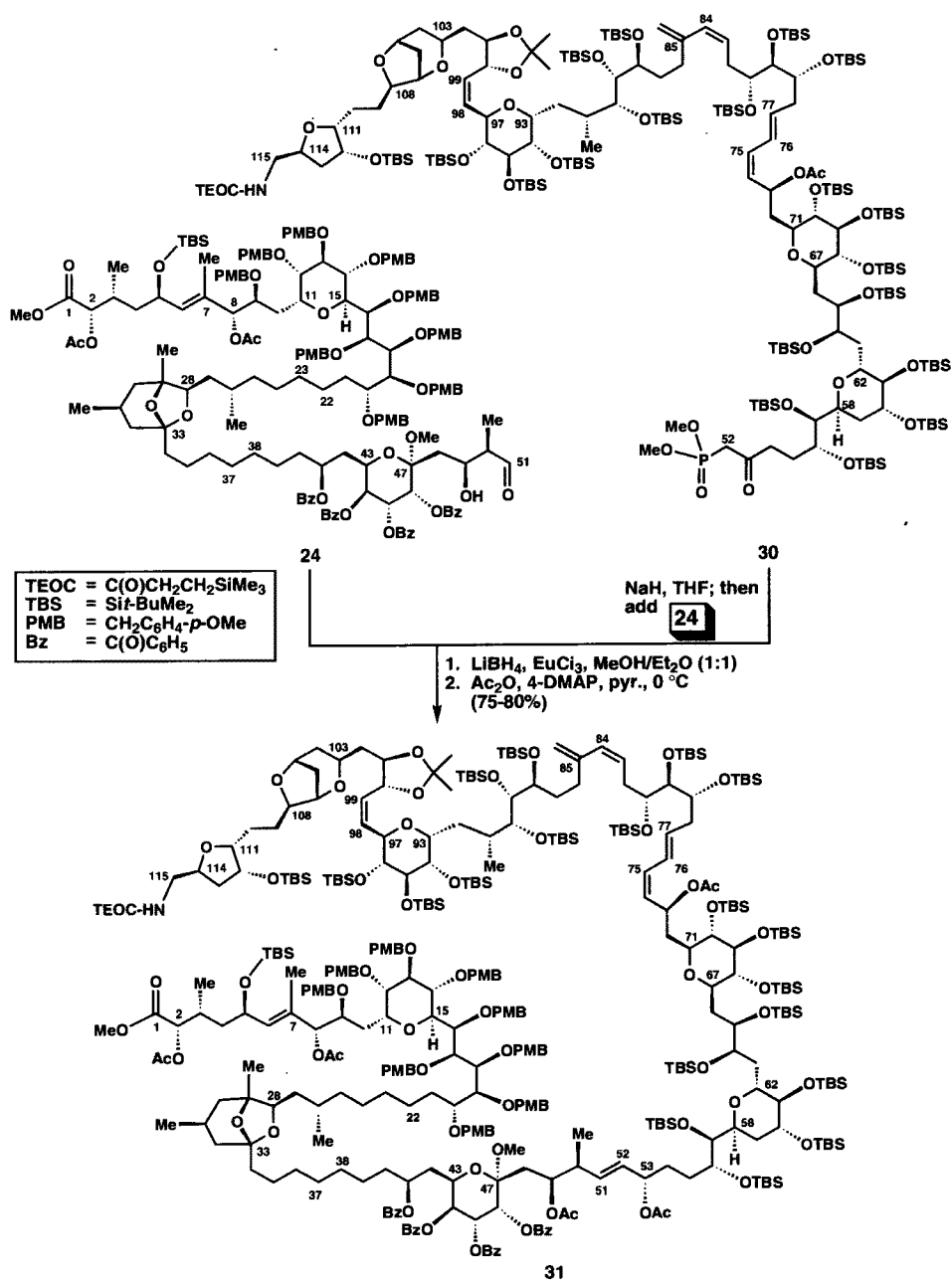
11

duced during this construction as individual units from the Matteson and the phosphonate reagents, respectively.

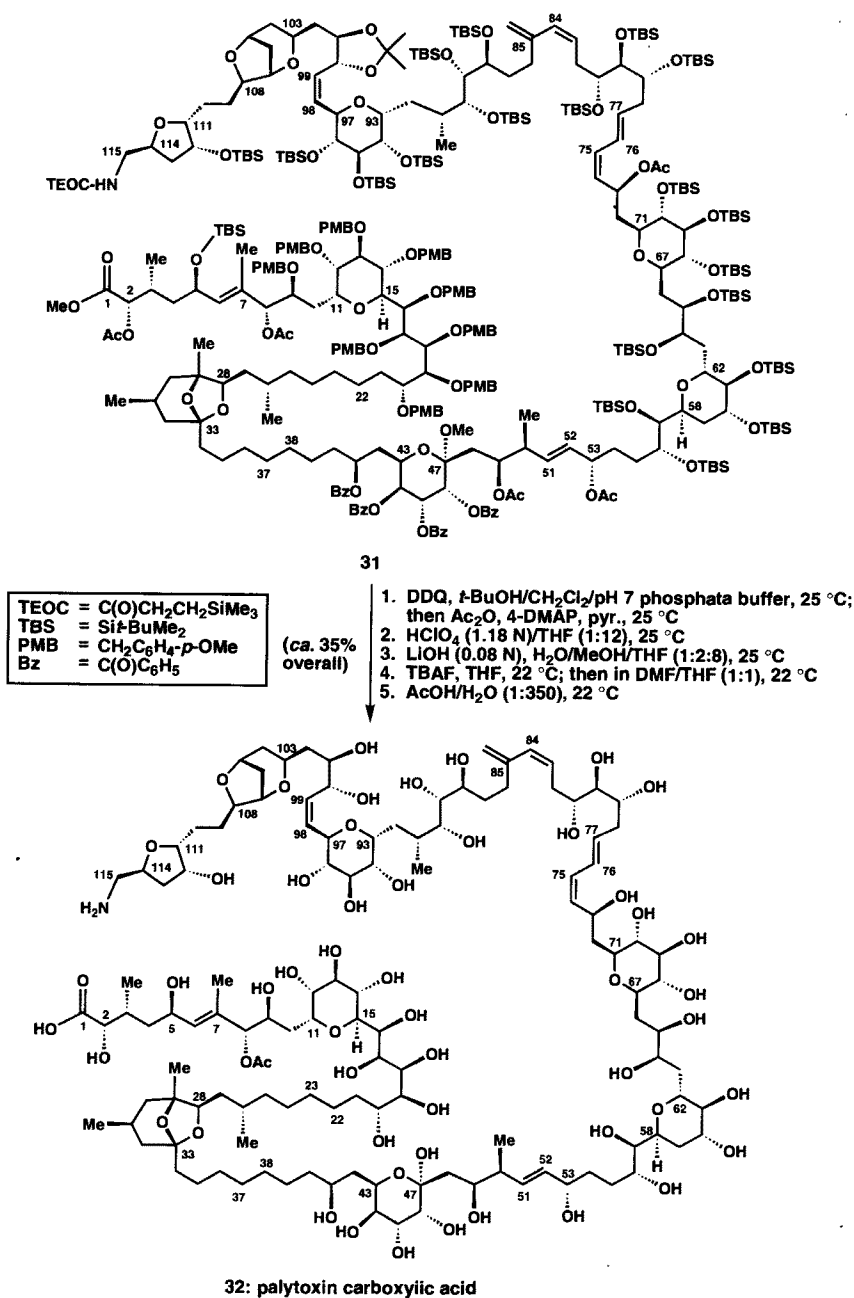
We have now reached a crucial stage in the palytoxin synthesis: the union of two large fragments and the problems usually associated with such relatively high molecular weight organic compounds. It is a testimony to the power of the ketophosphonate-aldehyde condensation reaction²³ and the experimental skills of the Kishi group that the coupling of ketophosphonate **30** and aldehyde **24** proceeds efficiently. Under standard basic conditions (NaH, THF), the desired *trans*- α,β -unsaturated ketone was obtained in 75–80% yield as a single geometrical isomer (see Scheme 9). Reduction (NaBH₄–EuCl₃, MeOH–ether) of the C-53 ketone carbonyl, followed by acetylation, results in the formation of allylic acetate **31**. The reduction of the C-53 ketone under the specified conditions proceeds in quantitative yield and with better than 5:1 stereoselectivity in favor of the indicated and desired isomer. The acetylation step proceeds in 90% yield.

The next major obstacle is the successful deprotection of the fully protected palytoxin carboxylic acid. With 42 protected functional groups and eight different protecting devices, this task is by no means trivial. After much experimentation, the following sequence and conditions proved successful in liberating palytoxin carboxylic acid **32** from its progenitor **31** (see Scheme 10): (a) treatment with excess 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in *tert*-butanol/methylene chloride/phosphate buffer pH 7.0 (1:8:1) under sonication conditions, followed by peracetylation (for convenience of isolation); (b) exposure to perchloric acid in aqueous tetrahydrofuran for eight days; (c) reaction with dilute lithium hydroxide in H₂O–MeOH–THF (1:2:8); (d) treatment with tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran first, and then in THF–DMF; and (e) exposure to dilute acetic acid in water (1:350) at 22°C. The overall yield for the deprotection sequence (**31** → **32**) is *ca.* 35%.

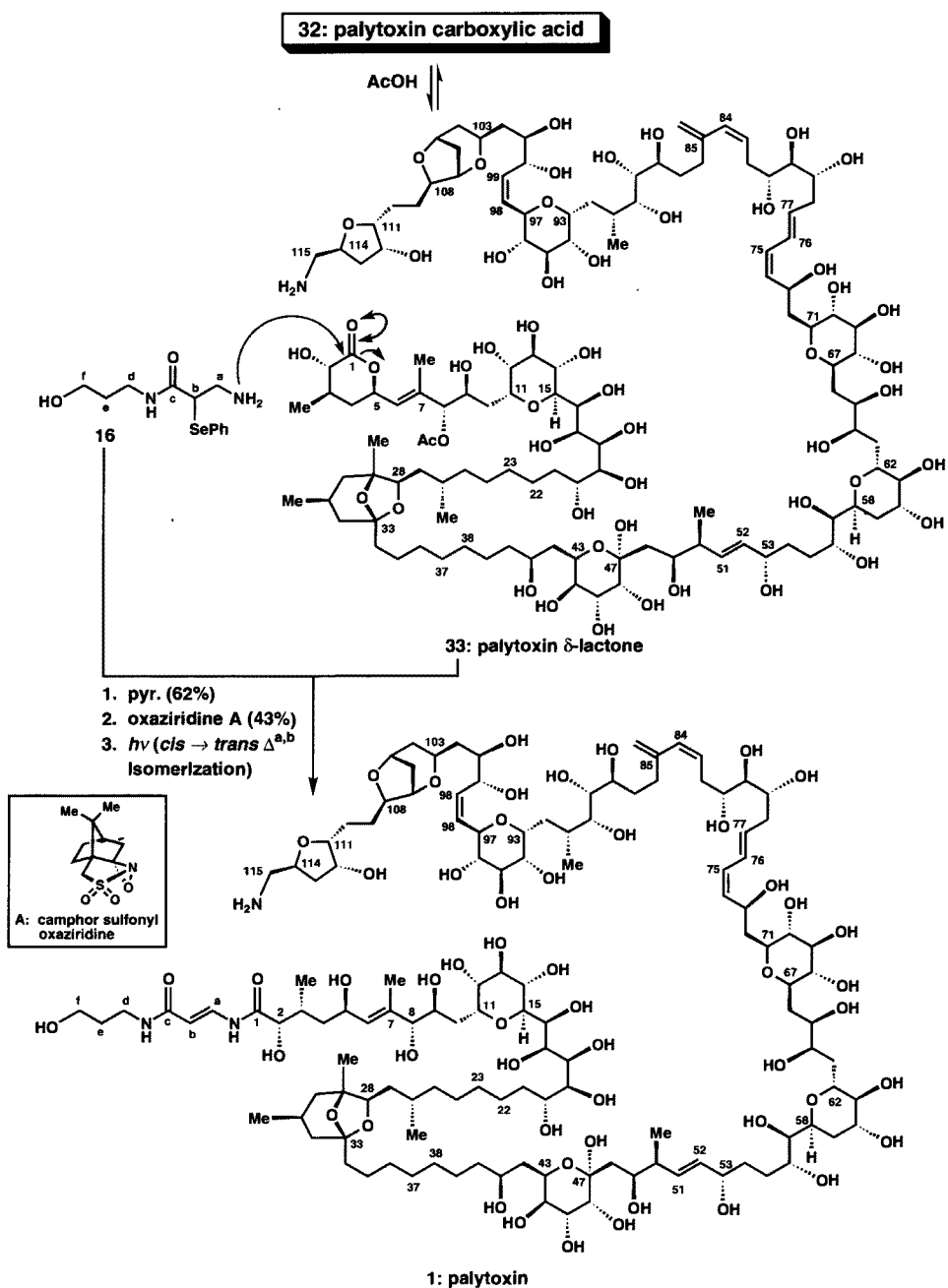
The final stages of Kishi's palytoxin synthesis involve the attachment of the *N*-acyl vinylogous urea side chain to C-1 of palytoxin carboxylic acid (**32**), a task that proved quite challenging and required the development of special methods. Among these, the most applicable to this synthesis involved the introduction of a side chain carrying a latent double bond in the form of a phenylselenenyl group. Thus, reaction of a mixture of palytoxin carboxylic acid and palytoxin δ -lactone, easily formed from palytoxin carboxylic acid by the action of acetic acid, with the C_a–C_f amine **16** (see Scheme 11) in pyridine at ambient temperature furnishes the corresponding C-1 amide in 36% yield (62% based on recovered palytoxin carboxylic acid). Oxidation of the phenylselenenyl group by Davis's (camphorsulfonyl)oxaziridine²⁴ (see (A), Scheme 11) is accompanied by spontaneous *syn*-elimination of the resulting selenoxide, affording a 3:2 mixture of *trans*- and *cis*-*N*-acyl vinylogous ureas in 43% total yield. The major isomer (*trans*- $\Delta^{a,b}$) of this mixture is palytoxin, and is identical to the authentic natural product.



Scheme 9. Coupling of key intermediates **24** and **30** and synthesis of fully protected palytoxin carboxylic acid **31**.



Scheme 10. Deprotection of **31** and synthesis of palytoxin carboxylic acid **32**.



Scheme 11. Construction of the *N*-acyl vinylglycine and synthesis of natural palytoxin (1).

Photochemical equilibration of the 3:2 stereoisomeric mixture of *N*-acyl vinylogous ureas in DMF by irradiation at 300 nm in a Rayonet reactor equipped with a stannous chloride filter solution at 37°C for 4 h leads to a 6:1 mixture of *trans*- $\Delta^{a,b}$ and *cis*- $\Delta^{a,b}$ palytoxins. The total synthesis of palytoxin (**1**) is now complete.

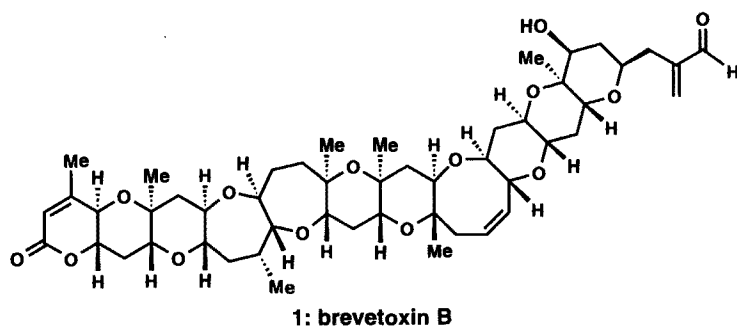
36.4 Conclusion

The total synthesis of palytoxin (**1**) is a landmark scientific achievement. It not only extended the frontiers of target-oriented synthesis in terms of the size and complexity of the molecules, but also led to new discoveries and developments in the areas of synthetic methodology and conformational analysis. Among the most useful synthetic developments to emerge from this synthesis include the refinement of the $\text{NiCl}_2/\text{CrCl}_2$ -mediated coupling reaction between iodoolefins and aldehydes, the improvements and modifications of Suzuki's palladium-catalyzed diene synthesis, and the synthesis of *N*-acyl vinylogous ureas.

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K. C. Nicolaou (1995)

Brevetoxin B

37.1 Introduction

Brevetoxin B (**1**) is a marine neurotoxin associated with the “red tide” catastrophes that periodically occur along coastal areas around the world and are responsible for massive killings of fish and other marine life, as well as human poisoning.¹⁻⁴ The term *red tide* describes seawater discolored by vast blooms of monocellular algae (phytoplankton), which constitute the base of the marine food chain. The name derives from the red coloration usually accompanying such occurrences, although the red tides may often be brown, green, or even colorless. The story of brevetoxin B (**1**) may be as old as 1000 B.C., for a passage in the Bible mentions an event that some believe might have been the first recorded incident of a red tide:

“... and the waters that were in the river were turned to blood. And the fish that were in the river died; and the river stank and the Egyptians could not drink of the water of the river ...”
Exodus 7:20-21

In more recent times, red tide incidents and poisonings have been recorded with an alarming increase in frequency. In 1793, Captain George Vancouver and his crew suffered poisoning during a red tide episode in British Columbia after consuming seafood from an area now known as Poison Cove; they then learned that the native Indians considered it forbidden to eat fish during such red tide phenomena. In 1972, a huge red tide was observed along the New England coast stretching from Maine to Massachusetts shortly after a major hurricane that presumably carried the poisonous algae from the Gulf of Mexico to the northeast coast

where favorable conditions allowed their rapid growth. During the same year, a costly red tide catastrophe occurred off the coast of Japan near the Seto Inland Sea, killing over 500 million dollars worth of caged yellowtail fish. In another episode, a massive human poisoning incident was recorded in Canada in 1987, during which victims complained of vomiting, diarrhea, disorientation, and abdominal cramps. The incident was later traced to poisoned mussels from Prince Edward Island where a red tide was in full bloom. In the same year, another disastrous event linked to red tide phenomena took place in which 14 humpback whales died suddenly and unexpectedly in Cape Cod, Massachusetts. In 1991, a bizarre incident was observed in which hundreds of sick and dying pelicans were found on the beaches of California near Monterey. Again, this tragedy was later traced to a red tide occurrence.

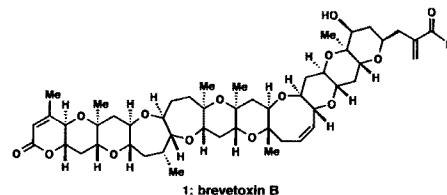
A most striking disaster took place off the east coast of the United States from 1987 to 1988 (right after the humpback whale episode) in which 760 bottlenose dolphins were found dead along the beaches stretching from New Jersey to Florida. This poisoning was traced to red tides caused by blooms of the dinoflagellate *Ptycodiscus brevis* Davis (*Gymnodinium breve* Davis), the alga responsible for the secretion of brevetoxins, a family of neurotoxins. Such incidents provide clear evidence of the dangers to the marine environment posed by these organisms, whose rapid and uncontrollable growth has been linked to oceanic pollution by humans.

Within the brevetoxin family, brevetoxin B (**1**) occupies a position of some historical significance, for it was the first member to be discovered.⁵ Brevetoxin B and its relatives are potent, lipid-soluble neurotoxins that exert their biological effects by binding to sodium channels of neurons, keeping them open, thereby causing depolarization of the cell membrane. Using a combination of spectroscopic and X-ray crystallographic methods, the groups of Lin, Nakanishi, and Clardy uncovered the remarkable structure of the brevetoxin B molecule in 1981.⁵ The complex molecular framework of compound **1** arises from the folding of a single carbon chain into a web of eleven rings fused together with interesting regularity. This regularity allows each ring to include an oxygen atom and each fusion to consist of a C–C bond separating two adjacent ring oxygens. All substituents on the ring junctions flanking the oxygens are *syn* to each other with the exception of the last one on ring K, which is *anti*. Brevetoxin B is composed of only carbon, hydrogen, and oxygen, and is distinguished by twenty-three stereocenters, three carbon–carbon double bonds, and two carbonyl groups. Interestingly, the polycyclic skeleton of brevetoxin B, which comprises a δ -lactone ring, seven tetrahydropyran rings, two oxepane rings, and a didehydrooxocane ring, is reminiscent of a ladder, a consequence of the *trans*-fusion of the eleven contiguous ether rings. Although the bis(oxepane) region (see rings D and E in structure **1**) confers some degree of flexibility to the natural product, brevetoxin B is a rather rigid molecule.

The striking constitution of brevetoxin B, unprecedented at the time of its discovery in 1981, presents a formidable challenge to organic synthesis. The unique and fascinating molecular architecture of brevetoxin B (**1**), its association with the red tide catastrophes, its potent biological activity, and the prospects for expanding the arsenal of synthetic methods all contributed in roughly equal measure to our decision to pursue a total synthesis of **1**. This chapter addresses the efforts that culminated in the total synthesis of brevetoxin B (**1**).⁶

37.1.1 *The Invention and Development of New Synthetic Methods*

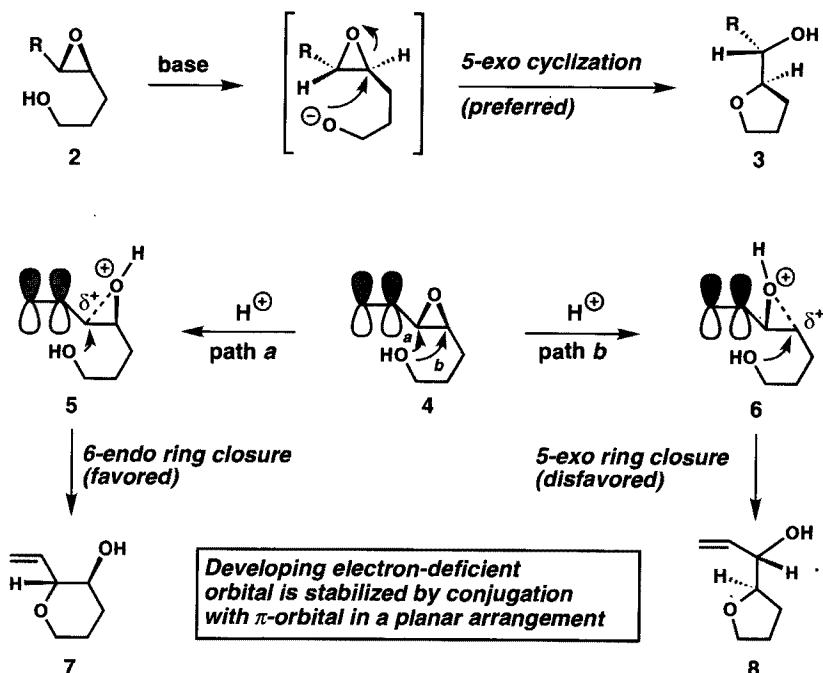
In order to follow and better appreciate the logic of the retrosynthetic analysis of brevetoxin B (**1**), we will discuss first the invention and development of new synthetic methods specifically designed for the total synthesis of brevetoxin B. We will then address the evolutionary process of retrosynthetic analysis and strategy design that led to the successful approach to brevetoxin B (**1**). We shall discuss separately, and in the following order, the methods developed for the construction of six-membered ring ethers (tetrahydropyrans), eight-membered ring ethers with a double bond (didehydrooxocanes), and seven-membered ring ethers (oxepanes) of the type found in brevetoxin B (**1**).



a. Tetrahydropyran Systems

In order to overcome the special problems posed by brevetoxin B's tetrahydropyran systems, the decision was made to develop and test regio- and stereoselective ring closures employing two types of substrates: hydroxy epoxides and hydroxy α,β -unsaturated esters. The basic concepts of these reactions are shown in Schemes 1 and 2, respectively.

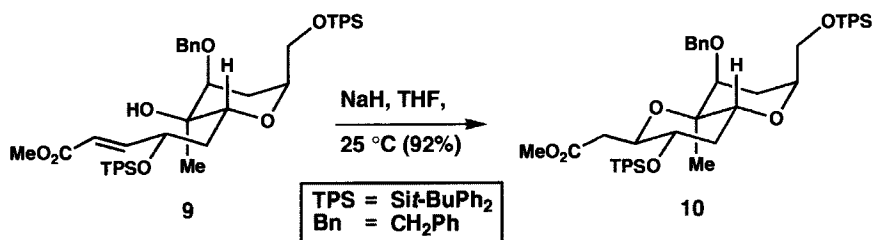
The opening of an oxirane ring by an internal oxygen nucleophile is an effective process for the construction of *O*-heterocycles;⁷ the facility of this process is intimately related to the ability of the cyclization substrate to assume a conformation in which the attacking nucleophile and the breaking oxirane C-O bond are collinear.^{8,9} This process is stereospecific, proceeding with inversion of configuration, at the oxirane carbon, and can be highly regioselective. For instance, if side chain R in generic epoxy alcohol **2** (Scheme 1) is saturated, a 5-*exo* cyclization leading to the formation of the smaller five-membered *O*-heterocycle **3** is generally preferred.⁹ Nevertheless, the hydroxy epoxide cyclization strategy can be effective in the synthesis of pyran rings if a carbon-carbon double bond is simply placed at the site adjacent to the oxirane ring (see **4**, Scheme 1), and if the cyclization reaction is conducted in the presence of an acid catalyst. This simple strategy is based on



Scheme 1. 6-endo-Activated hydroxy epoxide cyclization for the construction of tetrahydropyrans.

the premise that the oxonium ion resulting from protonation of the epoxide oxygen will seek stabilization by withdrawing electron density from the site that can better accommodate electron-deficient character, namely the site adjacent to the electron-rich π bond. The transition state associated with path *a* (see structure **5**, Scheme 1) would thus be expected to be of lower energy than the transition state for path *b* (see structure **6**, Scheme 1), thereby favoring the formation of the desired six-membered ring system **7** by means of a 6-endo cyclization. This pyran ring forming strategy has been studied in some detail;¹⁰ it is noteworthy that the cyclization event proceeds with inversion of configuration at carbon *a* and that selectivity for the 6-endo pathway is usually excellent.

The intramolecular Michael addition¹¹ of a nucleophilic oxygen to an α,β -unsaturated ester constitutes an attractive alternative strategy for the synthesis of the pyran nucleus, a strategy that could conceivably be applied to the brevetoxin problem (see Scheme 2). For example, treatment of hydroxy α,β -unsaturated ester **9** with sodium hydride furnishes an alkoxide ion that induces ring formation by attacking the electrophilic β -carbon of the unsaturated ester moiety. This base-induced intramolecular Michael addition reaction is a reversible process, and it ultimately affords the thermodynamically most stable product **10** (92 % yield).



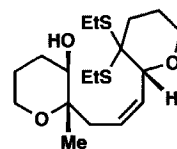
Scheme 2. Intramolecular conjugate addition for the construction of tetrahydropyrans affords the thermodynamically most stable isomer.

b. Didehydrooxocane Systems

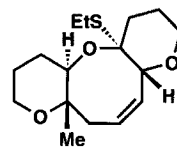
The difficulties inherent in the construction of seven-membered oxepane and eight-membered didehydrooxocane rings were recognized at the outset. When strategies for the synthesis of the brevetoxins were considered, there was a paucity of general synthetic methodology for the construction of medium-sized cyclic ethers. Our brevetoxin synthetic studies were thus motivated, to a significant extent, by the expectation that these novel natural products would inspire creative and general solutions to the synthesis of medium-ring ethers.

Of the medium rings (seven- to eleven-membered), the eight-membered ring is one of the most strained and difficult to construct owing primarily to the following factors:¹² (1) entropic disfavor, (2) bond opposition forces because of imperfectly staggered conformations (Pitzer strain), (3) bond angle deformations (Baeyer strain), and (4) destabilizing transannular interactions (i.e. repulsive interactions between atoms across the ring that develop when such groupings are forced into proximity). Although much effort has, in recent years, been devoted to the development of general strategies for the synthesis of eight-membered oxacycles¹³ and carbocycles,¹⁴ precedent for the assembly of the didehydrooxocane system (i.e. ring H in **1**) was clearly lacking when our studies began.

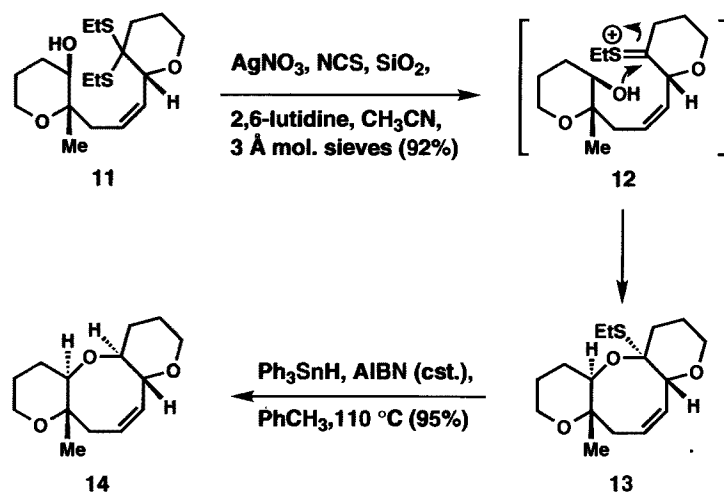
To those engaged in the synthesis of medium-rings, it is well known that the construction of eight-membered rings through the direct cyclization of acyclic molecules can be very difficult. Nonetheless, it was postulated that an eight-membered oxacycle could conceivably be produced through the intramolecular capture of a highly electrophilic function by an appropriately placed hydroxyl group, provided that sufficient conformational rigidity could be conferred upon the cyclization substrate. After a good deal of careful experimentation, it was found that treatment of hydroxy dithio-ketal **11** (see Scheme 3) with *N*-chlorosuccinimide (NCS) and AgNO₃ in the presence of 2,6-lutidine, dry silica gel, and 3 Å molecular sieves in acetonitrile at 25 °C results in the formation of didehydrooxocane **13** in 92 % yield.¹⁵ It is presumed that the com-



11



13



Scheme 3. Construction of didehydrooxocane systems by the hydroxy dithioketal cyclization.

bined action of NCS and AgNO_3 on **11** induces the formation of a transitory hydroxy thionium ion (see intermediate **12**), a highly reactive species that undergoes facile ring closure to oxocene **13**. It is important to note that the *cis* double bond plays a crucial role in the cyclization event by reducing rotational freedom in the cyclization substrate; in the absence of a *cis* double bond, ring closure does not occur. It is also noteworthy that silica gel is an important additive in this reaction; it brings about a roughly threefold increase in the rate of cyclization. A reasonable proposition is that adsorption of the cyclization substrate onto silica gel induces a conformational change that favors the cyclization event.

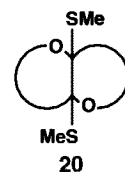
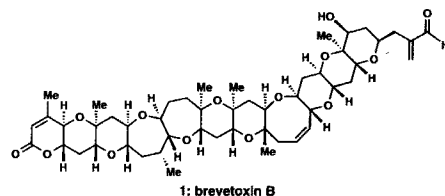
It is important to emphasize that the hydroxy dithioketal cyclization can be conducted under mild reaction conditions and can be successfully applied to a variety of substrates.¹⁵ However, the utility of this method for the synthesis of didehydrooxocane-containing natural products requires the diastereoselective, reductive removal of the ethylthio group. Gratifyingly, treatment of **13** with triphenyltin hydride and a catalytic amount of the radical initiator, azobisisobutyronitrile (AIBN), accomplishes a homolytic cleavage of the C–S bond and furnishes didehydrooxocane **14** in diastereomerically pure form (95 % yield), after hydrogen atom transfer.

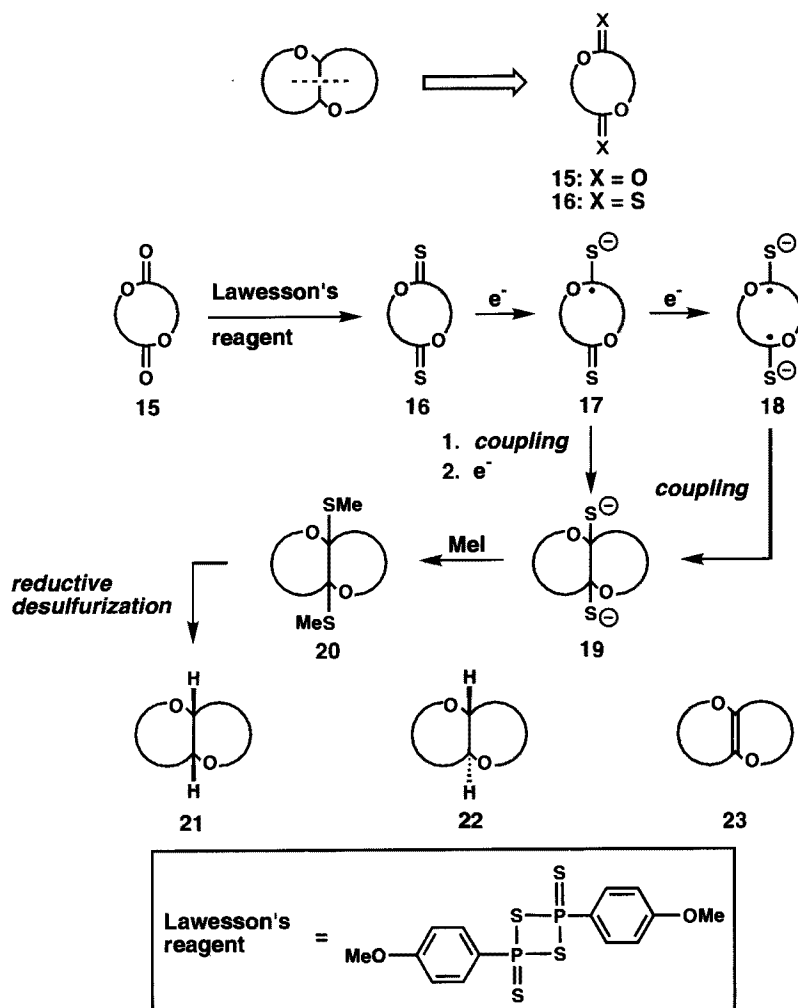
c. Oxepane Systems

With methods that performed so well in the construction of tetrahydropyran and didehydrooxocane rings in hand, it was natural to consider if these methods could also be applied to the synthesis of seven-membered oxepane rings. Although model studies revealed that seven-membered ether rings can be constructed in reasonable yields by means of the hydroxy epoxide¹⁶ and hydroxy dithioketal cyclization strategies, the opportunity to develop alternative ring-forming technologies was too tempting to pass by. It was therefore decided to defer a concentrated attack upon the brevetoxin B molecule until efficient and general strategies for the synthesis of seven-membered oxacycles could be developed.

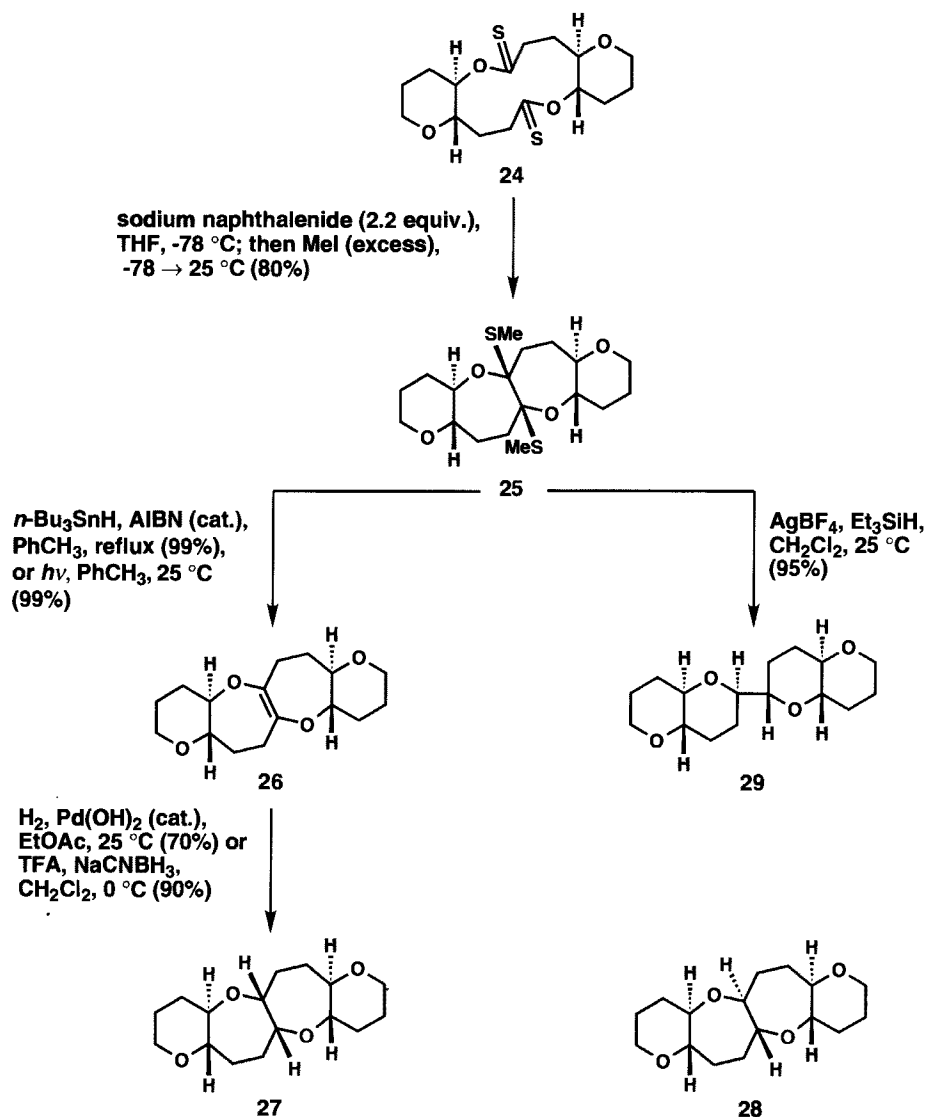
One of the more salient and synthetically challenging substructural features of the brevetoxin B molecule is the *trans*-fused [5.5.0] bicyclic ring framework, the bis(oxepane) system (see rings D and E in **1**). Careful consideration of this problem ultimately led to the rather daring, yet very attractive, proposal that it might be possible to construct a bis(oxepane) system by bridging a macrocyclic structure.¹⁷ This concept is simple and very appealing because the formation of one bond would result in the simultaneous formation of both oxepane rings. According to this proposal, both oxepane rings could be constructed in a single operation provided that a bond could be formed between the two sp^2 -hybridized carbon atoms of a macrocyclic bis(lactone) (**15**; X = O) or a macrocyclic bis(thiolactone) (**16**; X = S) (see Scheme 4); it was anticipated that these two carbon atoms could be joined under reducing (electron transfer) conditions. As matters transpired, application of this macrocycle bridging strategy to readily available macrodiolides (**15**; X = O), a process reminiscent of the classical acyloin condensation,¹⁸ proved unsuccessful, presumably due to the susceptibility of the intermediate vicinal alkoxides to destructive ring opening by C–O bond rupture. On the basis of this result, attention was turned to macrocyclic bis(thiolactones) (**16**; X = S). Relative to the C=O bond, the C=S bond possesses a lower reduction potential.¹⁹ Moreover, the stability and nucleophilicity of the thiolate ion, coupled with the versatility of organosulfur compounds with respect to further chemical manipulations, encouraged the employment of macrocyclic bis(thiolactones) in the conceptualized bridging reaction (Scheme 4). It was postulated that electron transfer to a thio-carbonyl group of a bis(thiolactone) (**16**) would furnish a radical anion (**17**) and that this species would then undergo conversion to a bridged product **19** as shown in Scheme 4. Alkylation of dianion **19** with methyl iodide was then expected to give the stable disulfide **20** which could subsequently be transformed to a variety of systems including *cis*- and *trans*-fused bicycles **21** and **22** and olefinic compound **23**.

In the event, macrocyclic bis(thiolactones) perform admirably in the macrocycle-to-bicycle bridging reaction (see Scheme 5).¹⁷ For example, the *cis*-fused tetracycle **25** can be produced, in 80 %

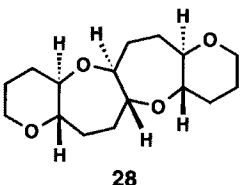
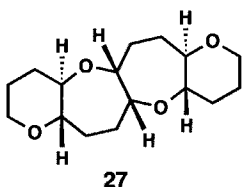
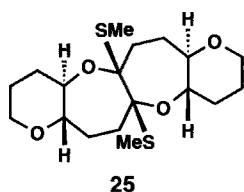




Scheme 4. Bridging macrocycles to bicycles: the concept.



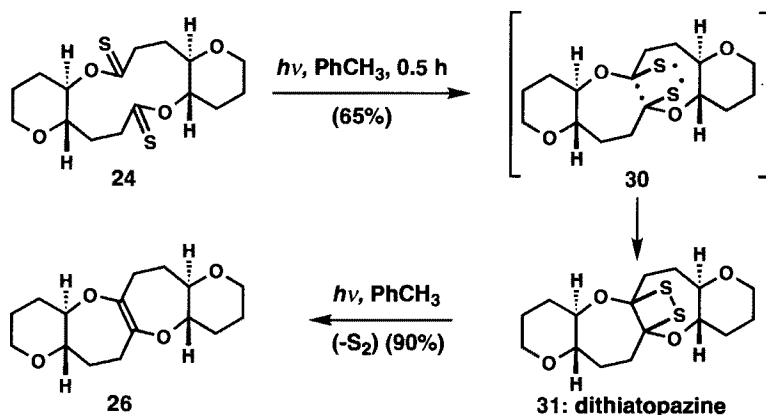
Scheme 5. Bridging macrocycles to form bicycles: the first successful experiments with bis(thiolactone) **24**. The terms bis(thiolactone) and dithiolactone are used in this chapter to describe compounds of type **24** even though such systems are sometimes referred to as dithionolactones or dithioxolactones.



yield, on treatment of bis(thiolactone) **24** with sodium naphthalene in THF at -78°C , followed by quenching with methyl iodide. The sequence of events leading from **24** to tetracycle **25** is initiated by a one-electron reduction of one or both of the $\text{C}=\text{S}$ bonds in **24** with sodium naphthalene. Interestingly, exposure of disulfide **25** to the action of tri-*n*-butyltin hydride and a catalytic amount of AIBN results in the formation of didehydrobis(oxepane) **26** in 99 % yield. Compound **26** could also be formed, in nearly quantitative yield, upon photolysis of disulfide **25**.

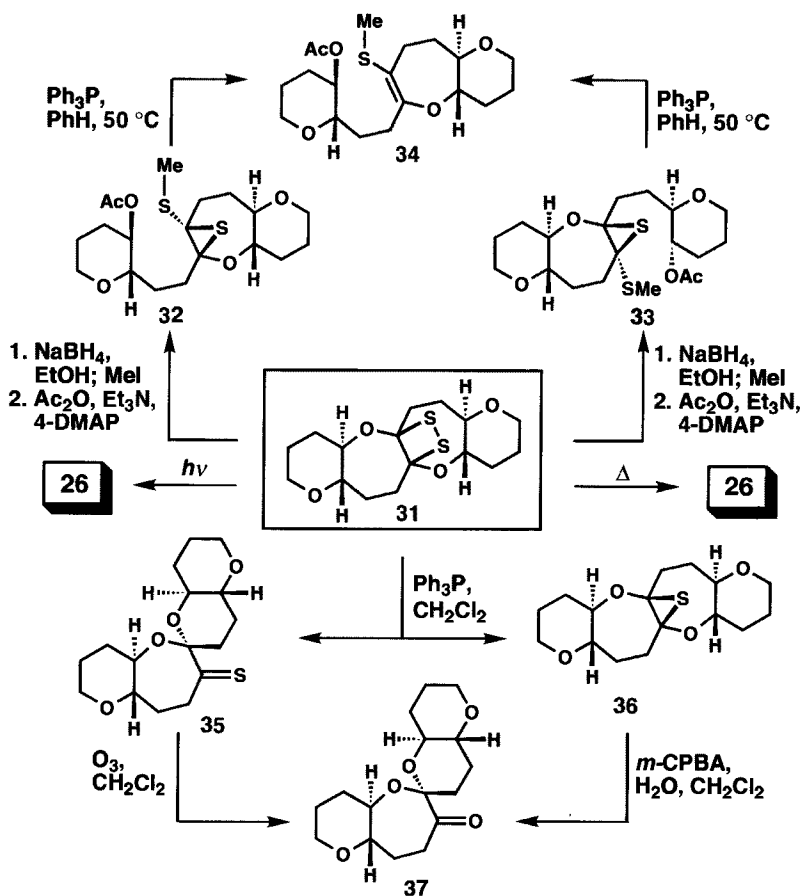
To enhance the utility of this ring-forming technology, conditions for the generation of the saturated derivatives **27** and **28** were sought. To this end, exposure of didehydrobis(oxepane) **26** to hydrogen and palladium hydroxide (Pearlman's catalyst) or to anhydrous trifluoroacetic acid (TFA) and excess sodium cyanoborohydride accomplishes the reduction of **26**, affording *cis*-fused bis(oxepane) **27** in yields of 70 and 90 %, respectively. To account for the reduction of **26** with sodium cyanoborohydride and TFA, it is proposed that an *exo*-selective reduction (i.e. *syn* to the hydrogen at the adjacent ring junction) of a transitory oxonium ion by the reducing agent takes place. Although it was originally reported that the action of triethylsilane and silver tetrafluoroborate on disulfide **25** affords *trans*-fused bis(oxepane) **28**,^{17a} it was later found that the interesting ring-contracted tetracycle **29** is, in fact, the only reduction product formed in this reaction. Despite several attempts, the desired *trans*-fused bis(oxepane) **28** could not be produced from either disulfide **25** or didehydrobis(oxepane) **26**; our search for a viable approach to the challenging *trans*-fused bis(oxepane) system continued.

The productive transformation of a macrocycle to a bicycle can also be executed simply by irradiating a bis(thiolactone). For example, irradiation of a solution of bis(thiolactone) **24** in toluene for



Scheme 6. Photo-induced bridging of bis(thiolactones): synthesis of dithiatopazine (**31**), the first stable 1,2-dithietane.

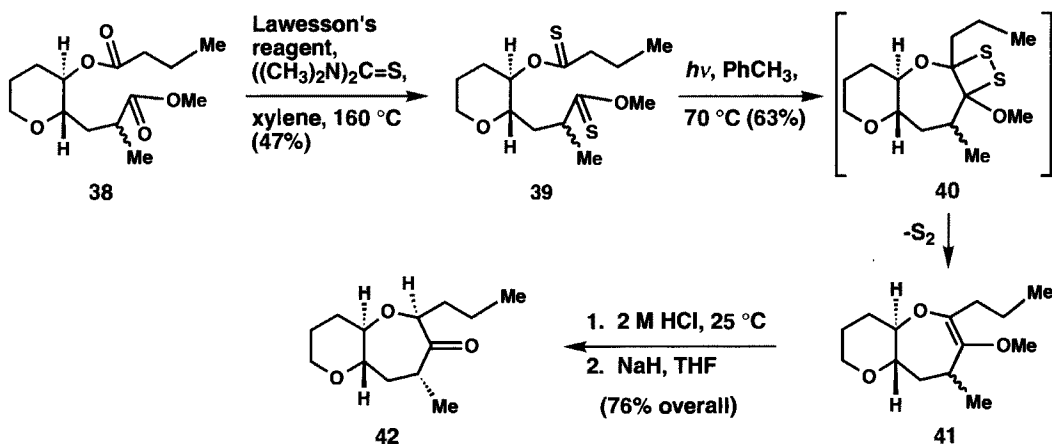
0.5 h furnishes the beautifully crystalline 1,2-dithietane **31** in 65 % yield (see Scheme 6).²⁰ This substance, termed dithiatopazine, is surprisingly stable and was the first of its kind to be isolated. For convenience, the intermediacy of the transitory species **30** was invoked to rationalize the transformation of bis(thiolactone) **24** to dithiatopazine (**31**); from **30**, compound **31** would form by a transannular coupling of radicals. A transannular reaction between excited and ground state thiocarbonyls is, however, a more plausible mechanistic pathway. Interestingly, further irradiation of dithiatopazine (**31**) induces the extrusion of disulfur to give didehydrobis(oxepane) **26** (90 % yield). The conversion of **31** to **26** can also be accomplished thermally or with a variety of reagents.²⁰ Dithiatopazine (**31**) participates in a variety of novel skeletal rearrangements and reactions, some of which are shown in Scheme 7.²⁰



Scheme 7. Novel chemistry of dithiatopazine (**31**).

As attractive as the transannular bridging of bis(thiolactones) to bicyclic bis(oxepane) frameworks is, our inability to convert the disulfide bridging product (see **25**, Scheme 5) to a *trans*-fused brevetoxin-type bis(oxepane) (see **28**) necessitated the development of a modified, stepwise strategy. This new stepwise approach actually comprises two very effective methods for the construction of cyclic ethers: the first of these is the intramolecular photo-induced coupling of dithioesters, and the second is the reductive cyclization of hydroxy ketones. We will first address the important features of both cyclization strategies, and then show how the combination of the two can provide an effective solution to the problem posed by *trans*-fused bis(oxepanes).

The photo-induced cyclization of a dithioester (see Scheme 8) is less productive than, but conceptually similar to, the chemistry outlined in Schemes 5 and 6. Diesters constitute the starting materials for this version of the photo-induced bridging strategy. Although there are several methods available to convert diesters or dilactones to the corresponding dithio counterparts, we have found Lawesson's reagent²¹ to be the most satisfactory; the thionation of diesters or dilactones with Lawesson's reagent is, in many contexts, an effective and reliable process. When diester **38** is treated with Lawesson's reagent in refluxing xylene, dithioester **39** is produced, albeit in modest yield (Scheme 8).²² Relative to bis(thiolactone) **24** (Scheme 6), dithioester **39** is certainly more conformationally flexible. Nevertheless, irradiation of a solution of **39** in toluene at 70 °C results in the formation of enol ether **41** (ca. 1:1 mixture of methyl epimers; 63% yield). It is presumed that irradiation of compound **39** affords a transitory diradical which undergoes rapid conversion to 1,2-dithietane **40**; under the reaction conditions, the lat-

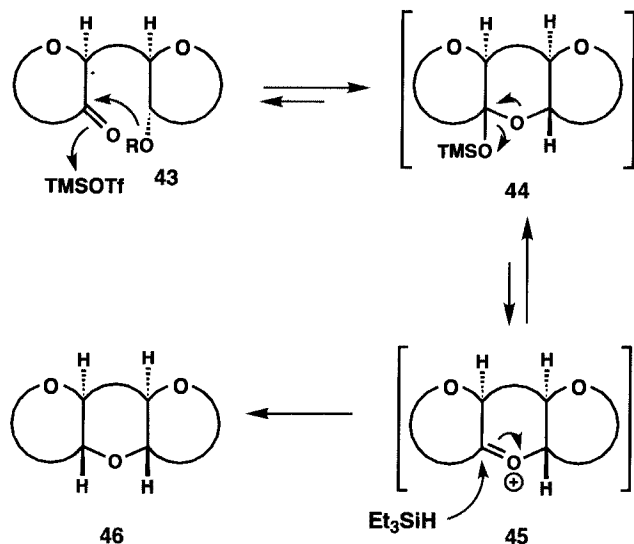


Scheme 8. Oxepane synthesis by photo-induced ring closure of dithioesters. The term dithioester is used in this chapter to describe compounds of type **39** even though such systems are sometimes referred to as dithionoesters or dithioxoesters.

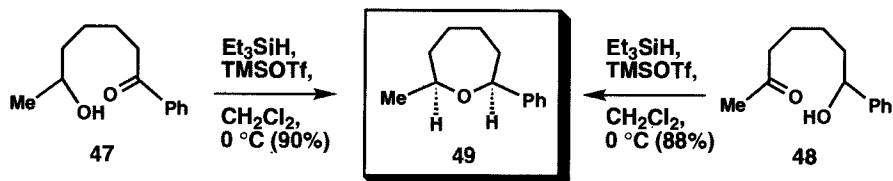
ter compound suffers irreversible loss of disulfur to give didehydrooxepane **41**. Although acid-induced hydrolysis of the methyl enol ether function in **41** provides ketone **42** as a ca. 1:1 mixture of methyl epimers, subsequent treatment of the epimeric ketones with sodium hydride in THF furnishes **42** as a single diastereoisomer (76% overall yield); the alkyl substituents flanking the ketone carbonyl in **42** are both equatorially disposed.

On the basis of model studies, it appears that a preexisting ring(s) in the cyclization substrate (e.g. **39**) is necessary for the success of this reaction type. Moreover, irradiation at elevated temperatures leads to cleaner reactions and higher yields, suggesting that thermal energy may be necessary to achieve the proper conformation for coupling to occur.²²

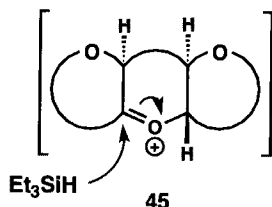
The reaction processes shown in Scheme 8 not only accomplish the construction of an oxepane system but also furnish a valuable keto function. The realization that this function could, in an appropriate setting, be used to achieve the annulation of the second oxepane ring led to the development of a new strategy for the synthesis of cyclic ethers: the reductive cyclization of hydroxy ketones (see Schemes 9 and 10).²³ The development of this strategy was inspired by the elegant work of Olah;²⁴ the scenario depicted in Scheme 9 captures its key features. It was anticipated that activation of the Lewis-basic keto function in **43** with a Lewis acid, perhaps trimethylsilyl triflate, would induce nucleophilic attack by the proximal hydroxyl group to give an intermediate of the type **44**.



Scheme 9. The reductive hydroxy ketone cyclization.



Scheme 10. Synthesis of compound **49** by the reductive hydroxy ketone cyclization method.

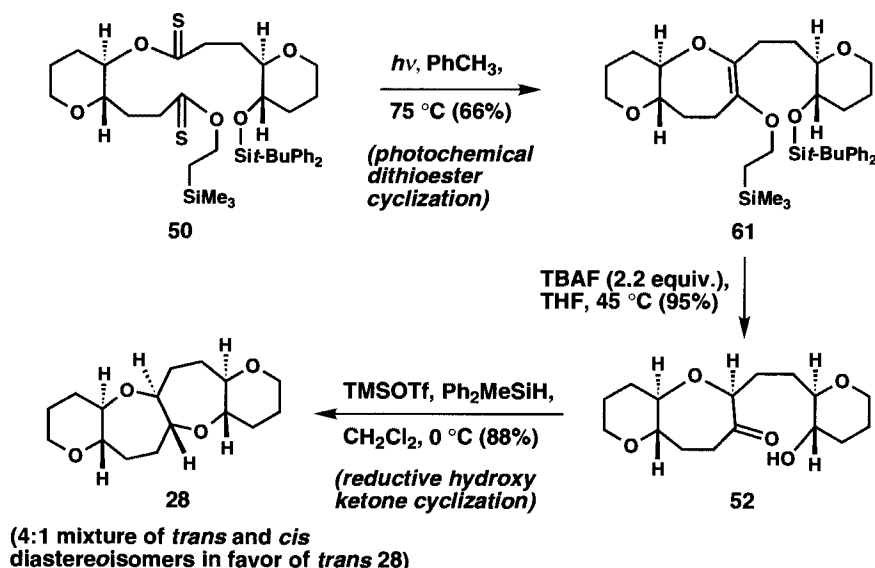


Under the reaction conditions, it is conceivable that the oxygen atom of the newly formed ring could initiate the formation of an oxonium ion such as **45**. Provided that this process is conducted in the presence of a reducing agent (e.g. triethylsilane), the reactive oxonium ion **45** could then undergo reduction to **46**. To test the feasibility of this reductive cyclization strategy, the reactions shown in Scheme 10 were carried out. Gratifyingly, exposure of hydroxy ketones **47** and **48** to excess triethylsilane and trimethylsilyl triflate in CH_2Cl_2 at 0°C results in the formation of oxepane **49** in excellent yield (88–90 %) and with complete *syn* diastereoselectivity.²³ This reductive cyclization strategy would thus appear to be ideally suited for the construction of cyclic ethers of the type found in brevetoxin B.

Having developed effective synthetic methodology for the construction of seven-membered cyclic ethers, we were confident that the problem of the *trans*-fused bis(oxepane) system could now be addressed on a solid foundation. It was our hope that the brevetoxin-type bis(oxepane) system could be assembled by a stepwise strategy utilizing both photochemical dithioester and reductive hydroxy ketone cyclization methods.

Dithioester **50** (see Scheme 11) was thus designed with the expectation that it could serve as a relevant model system to test the feasibility of this new stepwise approach.²³ In the event, irradiation of **50** in toluene at 75°C brings about the desired cyclization, affording didehydrooxepane **51** in 66 % yield. Simultaneous cleavage of the two silicon protecting groups with tetra-*n*-butylammonium fluoride (TBAF) then furnishes hydroxy ketone **52** (95 % yield), thus setting the stage for the reductive hydroxy ketone cyclization. On treatment of **52** with trimethylsilyl triflate and diphenylmethylsilane, the desired ring closure takes place, providing a 4:1 mixture of *trans* and *cis* ring fusion stereoisomers in favor of the desired *trans*-fused bis(oxepane) **28** (88 % total yield). At last, a strategy equal to the task of constructing the brevetoxin-type *trans*-fused bis(oxepane) substructure had been found.

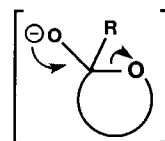
The assembly of medium-ring ethers using C–O or C–C bond forming protocols can be a profitable enterprise;¹³ nevertheless, it was of interest to determine if medium-ring ethers could be derived



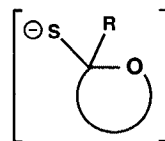
Scheme 11. Bis(oxepane) synthesis using a photochemical dithioester cyclization and a reductive hydroxy ketone cyclization.

from the corresponding lactones. The latter substances are extremely attractive as precursors to medium and large ring ethers because an abundance of effective methods are available for the synthesis of medium- and large-ring lactones:²⁵ the difficult issue of ring closure has already been resolved. The problem of transforming a medium-ring lactone to a medium-ring ether is one of reducing the oxidation state of the former.

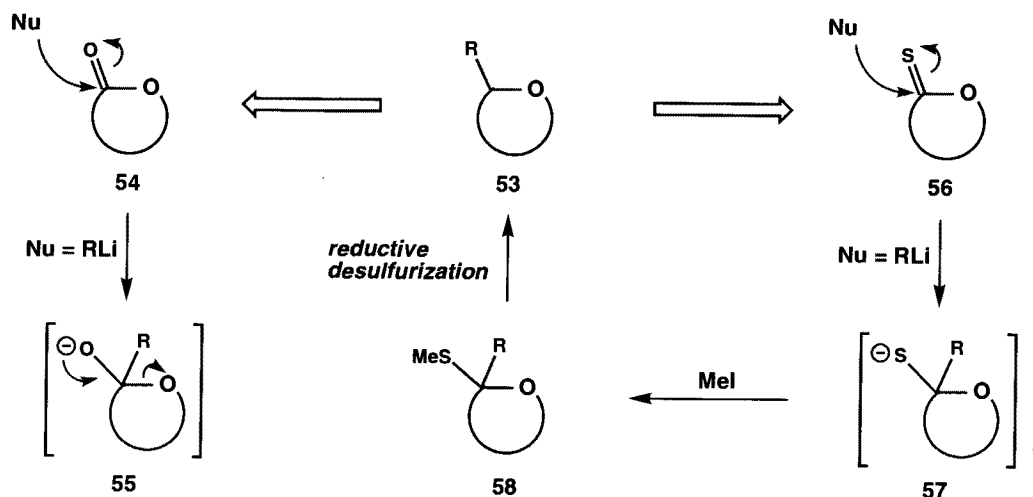
When a medium-ring lactone is exposed to a nucleophile, an organolithium reagent for example, the electrophilic lactone carbonyl suffers a nucleophilic attack to give a tetrahedral alkoxide intermediate (see **54** \rightarrow **55**, Scheme 12). Although **55** could, in principle, be trapped by various electrophiles and converted in a subsequent step to the corresponding cyclic ether **53**, medium- and large-ring tetrahedral alkoxides of type **55** are notoriously unstable species that collapse rapidly to give acyclic keto alkoxides. On the other hand, the tetrahedral intermediate that forms upon treatment of a thiolactone with a suitable nucleophile (see **56** \rightarrow **57**, Scheme 12) is relatively stable, particularly at low temperatures. It is therefore possible to capture the tetrahedral thiolate ion with electrophiles such as methyl iodide to give a monothio ketal (see **58**). Reductive desulfurization would then reveal the desired cyclic ether **53**.



55



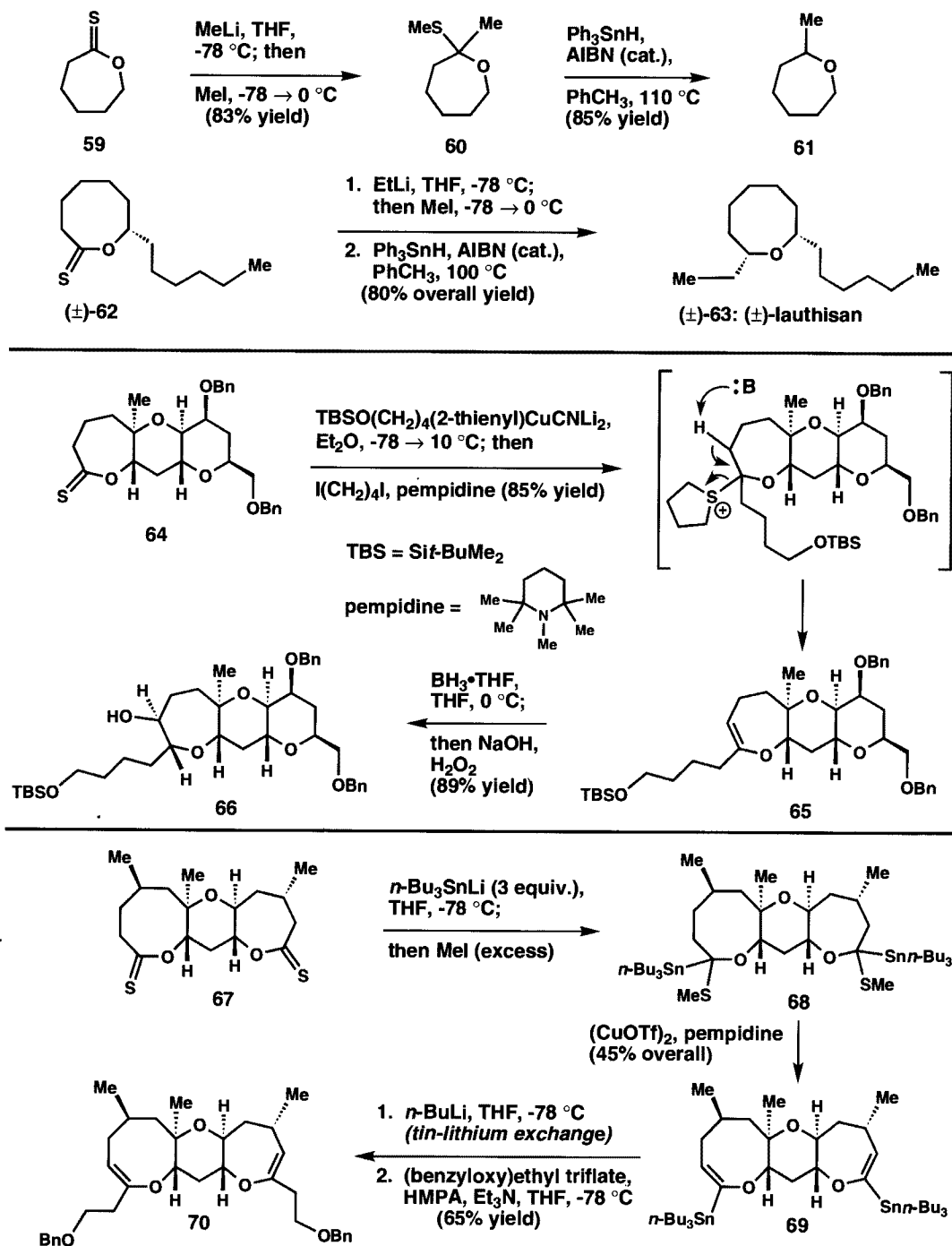
57



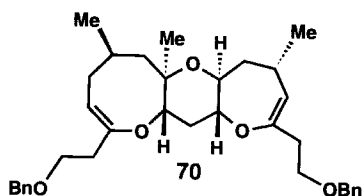
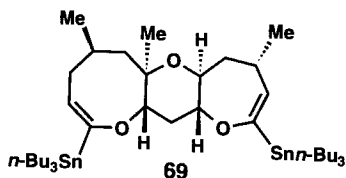
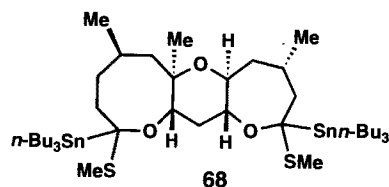
Scheme 12. Construction of cyclic ethers from thiolactones.

As amply demonstrated in Scheme 13, this strategy for the synthesis of seven- and eight-membered cyclic ethers is indeed an effective one. Treatment of thiocaprolactone (**59**), derived from the action of Lawesson's reagent on caprolactone, with methyllithium at -78°C in THF produces a tetrahedral thiolate ion which can be successfully trapped with methyl iodide to give monothio ketal **60** in 83 % yield.²⁶ In the presence of triphenyltin hydride and AIBN, the methylthio grouping in **60** is reductively cleaved, giving oxepane **61** in 85 % yield via a carbon-centered radical. Interestingly, when certain chiral thiolactones are subjected to this three-stage reaction sequence, the nucleophilic addition step and the subsequent reductive desulfurization proceed diastereoselectively. For example, only one monothio ketal diastereoisomer is observed after sequential treatment of racemic thiolactone **62** with ethyllithium and methyl iodide (see Scheme 13). Reductive removal of the methylthio group with triphenyltin hydride and a catalytic amount of AIBN also proceeds diastereoselectively, affording the natural product (\pm)-lauthisan [(\pm) -**63**] in 80 % overall yield.

The conversion of a thiolactone to a cyclic ether can also be used as a key step in the synthesis of functionalized, stereochemically complex oxacycles (see **64** \rightarrow **66**, Scheme 13). Nucleophilic addition of the indicated higher order cuprate reagent to the C-S double bond in thiolactone **64** furnishes a tetrahedral thiolate ion which undergoes smooth conversion to didehydrooxepane **65** upon treatment with 1,4-diiodobutane and the non-nucleophilic base 1,2,2,6,6-pentamethylpiperidine (pempidine).²⁷ Regio- and diastereoselective hydroboration of **65** then gives alcohol **66** in 89 % yield after oxidative workup. Versatile vinylstannanes can also be accessed from thiolactones.²⁸ For example, treatment of bis(thiolactone) **67** with



Scheme 13. Synthesis of cyclic ethers from thiolactones.

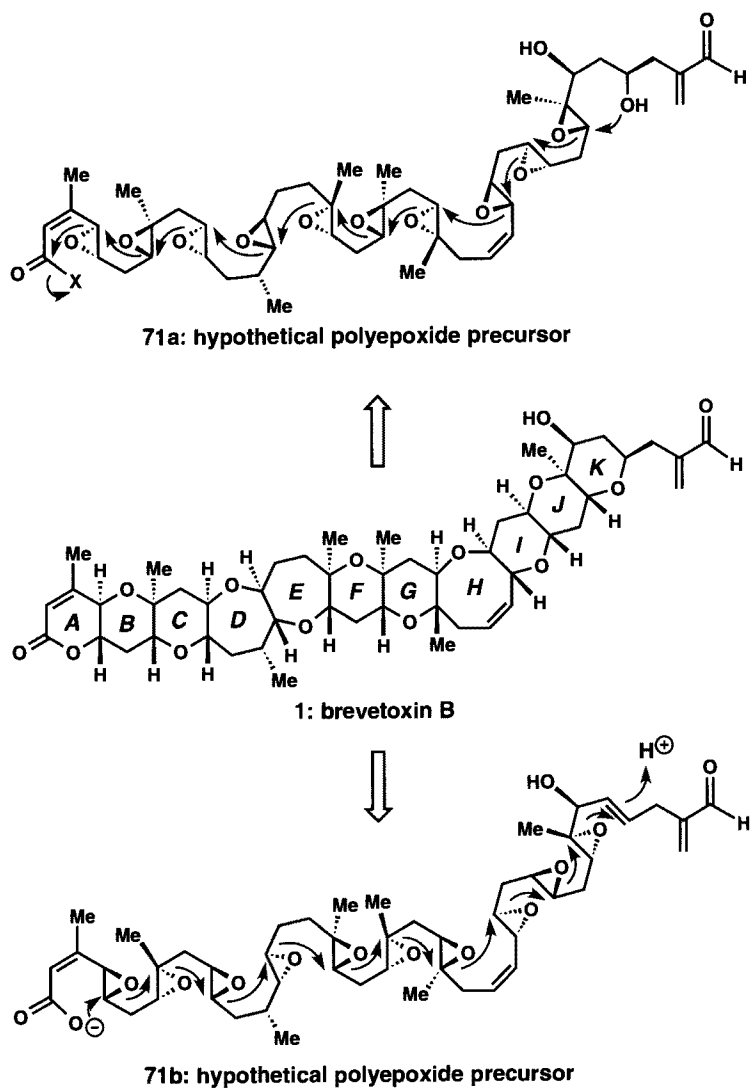


three equivalents of lithium tri-*n*-butylstannane²⁹ furnishes compound **68** after quenching with excess methyl iodide. Elimination of the methylthio functions with cuprous triflate and pempidine then affords bis(vinylstannane) **69** (45 % yield). Compound **70** can be produced in 65 % yield through alkylation of the bis(vinylstannane) reagent derived from **69** with (benzyloxy)ethyl triflate.

With a collection of methods for the construction of tetrahydropyran, oxepane, bis(oxepane), and didehydrooxepane frameworks at our disposal, we were confident that an assault upon the imposing brevetoxin B molecule could be mounted. In the sections that follow, we describe our first-, second-, and third-generation approaches to the synthesis of brevetoxin B (**1**). Although the first two approaches did not accomplish the total synthesis of the target, a number of effective reactions were developed, and the important information garnered helped to shape the development of the successful third-generation strategy.⁶ Because of its instructive nature, the chemistry of the unsuccessful approaches will also be addressed; however, we will only highlight important features of the first- and second-generation approaches. Only the third-generation approach will be discussed in detail.

37.2 Retrosynthetic Analysis and Strategy

The structure of brevetoxin B (**1**) is distinguished by a ladderlike array of eleven *trans*-fused six- to eight-membered cyclic ethers. The constitution of **1** may be formidable, but the particular arrangement of the contiguous ether rings is very interesting because the entire structure could conceivably arise in one dramatic event from the polyepoxide precursors **71a** or **71b** shown in Scheme 14.³⁰ Although these hypothetical biosynthetic pathways bear a close resemblance to Cane, Celmer, and Westley's unified proposal for the biosynthesis of the polyether ionophores such as monensin,³¹ the question as to whether nature employs any of these productive polycyclization cascades in the biosynthesis of brevetoxin B has not yet been experimentally answered.³² In spite of their productivity and aesthetic appeal, these concerted polycyclizations would be very difficult to execute in the laboratory. In addition to the difficulties inherent in the stereoselective synthesis of the requisite polyepoxides, there would be no way to enforce the desired regiochemical course of the individual ring closures. A more prudent and conservative pathway for a synthesis of brevetoxin B was, therefore, sought. Although the development of general utility methods for the construction of cyclic ethers provided a persistent driving force for our investigations, the total synthesis of brevetoxin B was always the primary objective. In the following subsections, we describe the evolution of synthetic studies which ultimately led to the first total synthesis of brevetoxin B (**1**).

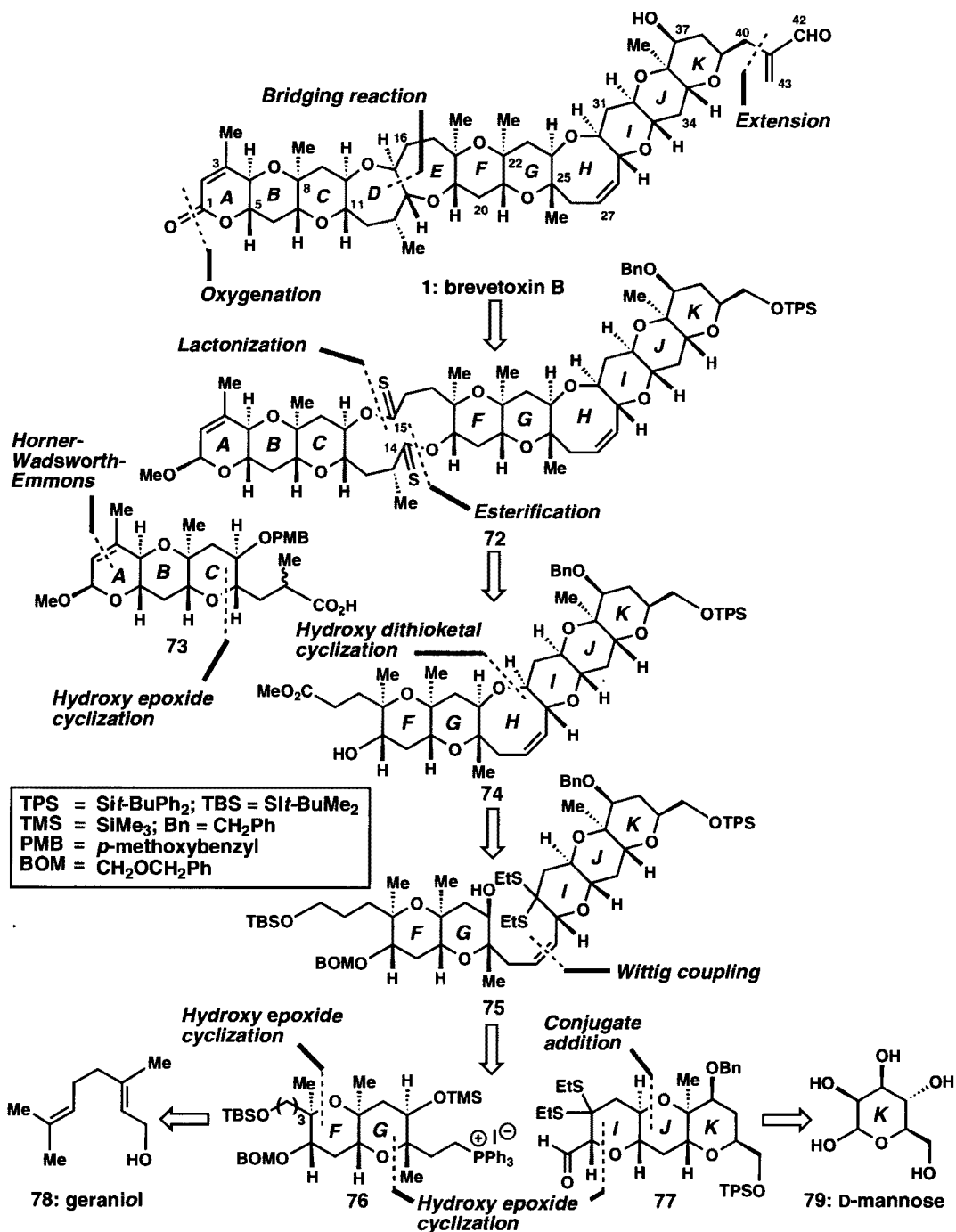


Scheme 14. Structure of brevetoxin B (**1**) and hypothetical polyepoxide precursors **71a** and **71b**.

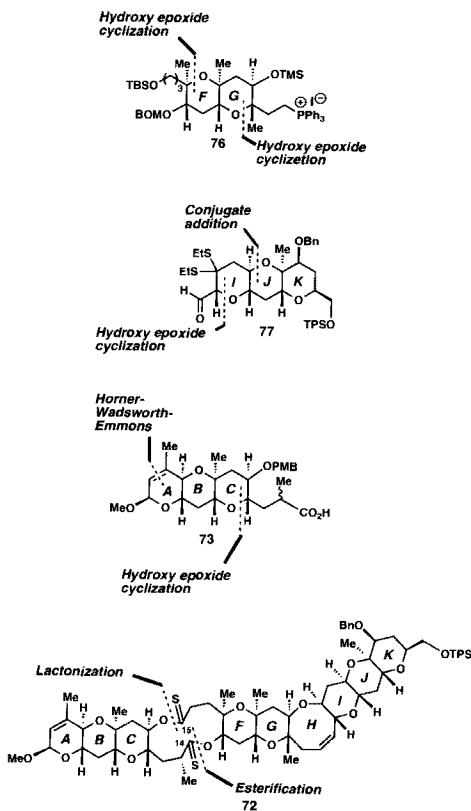
37.2.1 *The Triply Convergent Approach: The First-Generation Strategy*

Given the complexity of the brevetoxin B molecule, it was natural to consider various ways in which the natural product could be assembled in a convergent manner. Indeed, the desire to maximize convergency motivated the development of the strategy outlined retrosynthetically in Scheme 15. This strategy, the first-generation strategy, is based on the following three reaction processes, which were developed for the purpose of synthesizing brevetoxin B (**1**): (1) the bridging of macrocycles to form bicycles (see Schemes 4–6), (2) the facile cyclization of hydroxy dithioketals to form didehydrooxocane frameworks (see Scheme 3), and (3) the regio- and stereospecific cyclization of hydroxy epoxides for the construction of tetrahydropyran systems (see Scheme 1).

As shown in Scheme 15, retrosynthetic removal of the electrophilic groupings attached to the terminal rings of the natural product and retrosynthetic disassembly of the bis(oxepane) system provides bis(thiolactone) **72** as a potential precursor. It was anticipated that transannular bridging of the 12-membered bis(thiolactone) **72** would result in the formation of the carbon–carbon bond common to rings D and E. If successful, this maneuver would accomplish the simultaneous formation of two of the three medium-sized rings contained within brevetoxin B (**1**). A short sequence of functional group manipulations could then complete the synthesis of **1**. An attractive feature of this strategy is that compound **72** could, in principle, be assembled in short order from building blocks **73** and **74**. Compound **73** comprises rings A, B, and C of the natural product, and it derives from the corresponding δ -lactone (ring A).³³ It can be disconnected as indicated in Scheme 15. Compound **74**, the FGHIJK fragment, is an impressive molecular assembly. Although we feared that the strained didehydrooxocane ring in **74** would hinder any effort to construct this compound, we also had much confidence in the hydroxy dithioketal cyclization method (see Scheme 3). Indeed, the results of numerous cyclization experiments underscore the utility of this method for the construction of didehydrooxocane rings.¹⁵ Hydroxy dithioketal **75** thus emerges as a plausible precursor to compound **74**. It is important to note that the *cis* carbon–carbon double bond in **75** is a structural prerequisite for the crucial hydroxy dithioketal cyclization and is expressed in the natural product. The selection of this cyclization method is thus very logical because the structural element permitting the desired ring closure, namely the *cis* double bond, does not require subsequent modification. But in addition to its role in the construction of the didehydrooxocane ring of brevetoxin B, the *cis* double bond in compound **75** also provides a convenient opportunity to achieve significant structural simplification. Retrosynthetic cleavage of the *cis* double bond in **75** provides compounds **76** and **77** as potential precursors. In the synthetic direction, the convergent union of **76** and **77** by a *cis*-selective Wittig reaction could furnish hydroxy



Scheme 15. Retrosynthetic analysis of brevetoxin B (**1**): the first-generation approach.

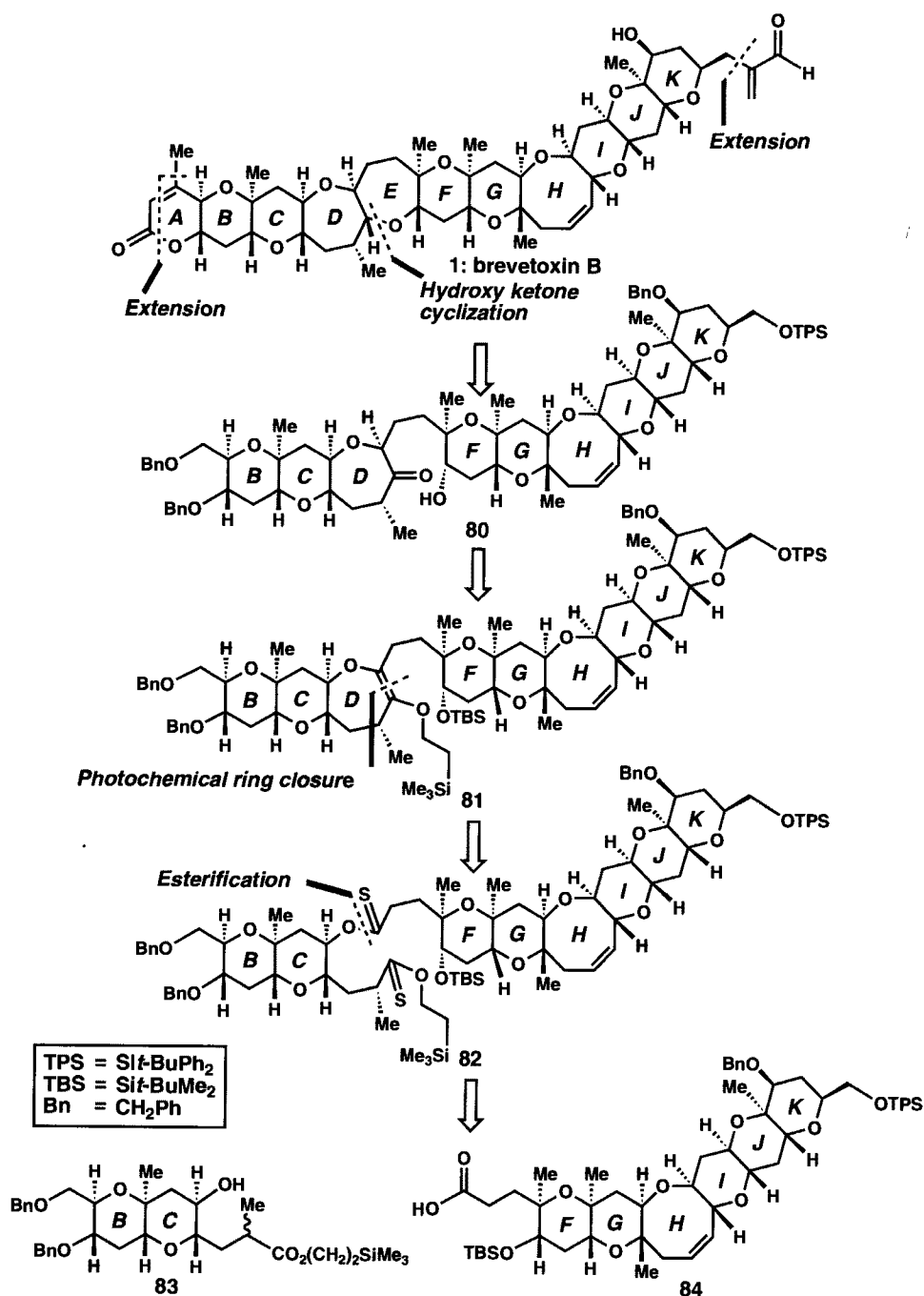


dithioketal **75**, after cleavage of the TMS ether. Syntheses of compounds **76** and **77** from the indicated precursors (**78** and **79**, respectively) by pathways utilizing intramolecular conjugate addition and hydroxy epoxide cyclization reactions could finally be envisioned.^{34,35} The synthetic problem is thus reduced to three building blocks of comparable complexity, compounds **73**, **76**, and **77**. These three building blocks account for eight of the eleven cyclic ethers found in brevetoxin B, and it was our hope that the remaining three oxacycles, rings D, E, and H, could be constructed by using a collection of reliable coupling and ring-forming reactions.

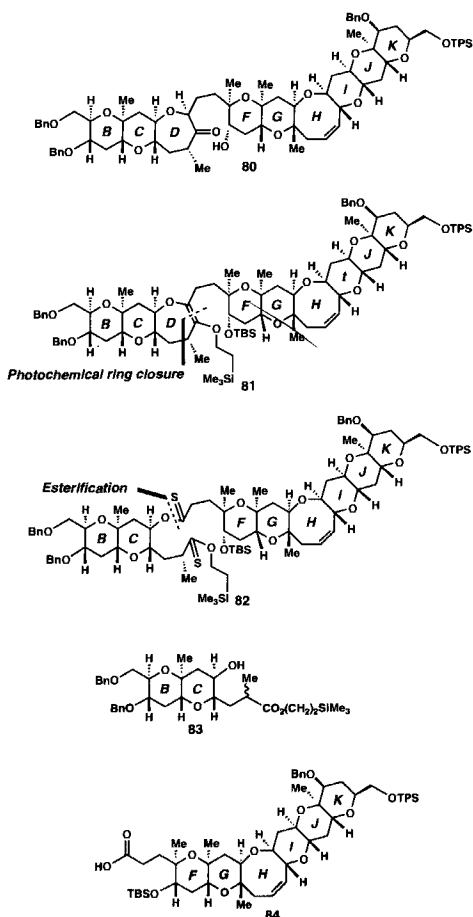
Efforts to implement this highly convergent strategy were initially rewarding. For example, the requisite building blocks, compounds **73**,³³ **76**,³⁴ and **77**,³⁵ could all be synthesized in optically active form by pathways that featured the effective 6-*endo* activated hydroxy epoxide cyclization method (see Scheme 1).¹⁰ In addition, the convergent Wittig reaction joining compounds **76** and **77**, the crucial hydroxy dithioketal cyclization forming the didehydrooxocane unit, and the construction of the polycyclic macrodilactone corresponding to **72** all proceeded relatively smoothly. Thus, a rather advanced stage in the synthesis could be reached virtually without incident. Unfortunately, however, all attempts to achieve the bis(thionation) of the macrodilactone precursor of compound **72** failed. In the presence of a large excess of Lawesson's reagent and at high temperatures, the C-15 (brevetoxin numbering) lactone carbonyl can be thionated. The lactone carbonyl flanked by the methyl group (C-14), on the other hand, defiantly resists the action of Lawesson's reagent, presumably due to its hindered nature. A variety of other Lawesson-type reagents were likewise unable to bring about the formation of the requisite bis(thiolactone) **72**, and we were thus forced to abandon this otherwise very attractive strategy.

37.2.2 Stepwise Bis(oxepane) Synthesis Approach: The Second-Generation Strategy

Having been unable to construct the fused oxepane rings in brevetoxin B simultaneously with the macrocycle bridging reaction, we elected to adopt a stepwise approach to the synthesis of the bis(oxepane) region (see Scheme 16). Like the first-generation approach, this new strategy defers the construction of oxepane rings D and E to an advanced stage in the synthesis and is highly convergent. On the basis of the successful transformations summarized in Scheme 11, it was our hope that the challenging bis(oxepane) substructure of the natural product could be assembled by a strategy that combines the effective dithioester cyclization reaction with the reductive hydroxy ketone cyclization reaction. Thus, retrosynthetic disassembly of the oxepane ring E in **1** in the indicated way provides hydroxy ketone **80** as a potential precursor (Scheme 16). In spite of its somewhat hindered nature, the D-ring keto function in **80** was



Scheme 16. Retrosynthetic analysis of brevetoxin B (**1**): the second-generation approach.



expected to participate in a reductive cyclization reaction with the F-ring secondary hydroxyl group, seven atoms removed, on treatment with trimethylsilyl triflate and triethylsilane (see Schemes 9–11). Annulation of the unsaturated δ -lactone representing ring A, elaboration of the unsaturated aldehydic side chain attached to ring K, and a deprotection step would then complete the synthesis of the natural product.

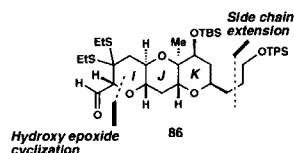
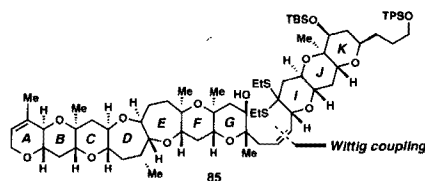
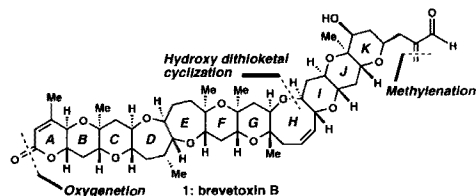
The D-ring keto group in **80**, the electrophile in the projected hydroxy ketone cyclization, could be unveiled upon fluoride-induced cleavage of the enol ether function in **81** (see **51** \rightarrow **52**, Scheme 11). The latter compound is poised for a productive retrosynthetic maneuver; disassembly of ring D in **81** in the manner illustrated uncovers dithioester **82**. Although the carbon chains bearing the two thiocarbonyl moieties are rather flexible, it was anticipated that irradiation of **82**, perhaps with some thermal assistance, would effect the desired ring closure to didehydrooxepane **81**. Our confidence in this transformation could be attributed to the successful ring closures presented in Schemes 8 and 11. An attractive feature of this ring-forming strategy is that the requisite dithioester is itself amenable to a productive retrosynthetic operation. For example, cleavage of the indicated C–O bond in **82** furnishes compounds **83** and **84** as potential precursors. In the synthetic direction, acylation of the free secondary hydroxyl in **83** with an activated ester derived from **84**, followed by bis(thionation) of the resulting diester, could give dithioester **82**. It will be noted that hexacyclic carboxylic acid **84** is very similar to compound **74**, a substance that we encountered previously (see Scheme 15). Convergent Wittig and hydroxy dithioacetal cyclization reactions could be used to fashion compound **84** from two building blocks representing the FG and IJK sectors.

It was gratifying to find that much of this strategy could be implemented without incident. The construction of key intermediates **83** and **84** proceeded rather smoothly as did the DCC-mediated acylation of **83** with **84**. Bis(thionation) of the diester then furnished dithioester **82**, setting the stage for the construction of the first oxepane ring. As expected, irradiation of **82** brought about the union of the two thiocarbonyl carbon atoms and furnished didehydrooxepane **81** (63% yield) after expulsion of disulfur. In the presence of tetra-*n*-butylammonium fluoride (TBAF), two of the three silicon protecting groups in **81** were cleaved, giving rise to hydroxy ketone **80** after diastereoselective protonation of the intermediate enolate. Although the reductive hydroxy ketone cyclization performed quite well in a variety of contexts,²³ all attempts to cyclize hydroxy ketone **80** in an analogous manner were unsuccessful; reduction of the D-ring keto function to the corresponding secondary alcohol was the only transformation observed. This most unfortunate result, in conjunction with the pitfall encountered during the first-generation campaign, required the development of a strategy that addressed the recalcitrant bis(oxepane) region at an earlier stage. As unpalatable as it was, we eventually realized that convergency would have to give way to linearity, at least partially.

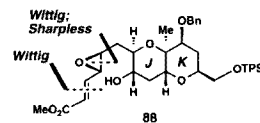
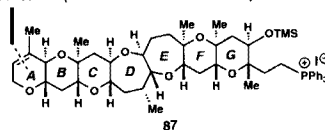
37.2.3 The Doubly Convergent Approach with Stepwise Formation of the Bis(oxepane) System: The Third-Generation Strategy

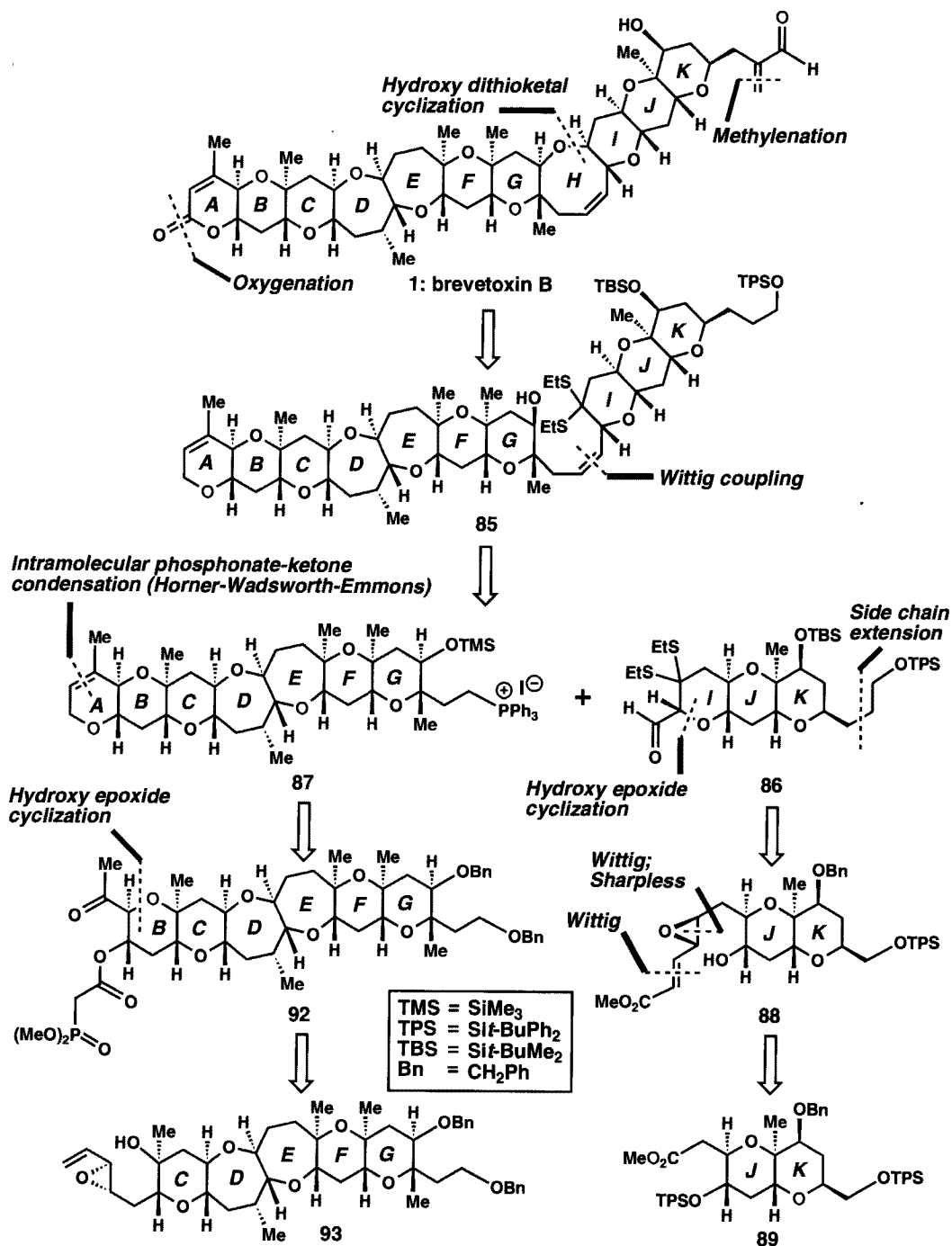
A third retrosynthetic analysis of brevetoxin B (**1**) will now be discussed in which a certain degree of convergency is sacrificed in order to circumvent the problems imposed by the bis(oxepane) region of the molecule. Schemes 17a–c outline this last retrosynthetic analysis. The reliability of the hydroxy dithioketal cyclization method (see Scheme 3) for the synthesis of didehydrooxocane frameworks fostered the proposal to reserve the anchor position for this process. The didehydrooxocane ring in brevetoxin B (ring H) was thus designated as the final ring to be constructed. Retrosynthetic cleavage of the indicated C–O bond in **1** and removal of the terminal electrophilic groupings reveal hydroxy dithioketal **85** as a plausible precursor. Conversion of the dithioketal function in **85** to a highly electrophilic thionium ion was expected to induce an intramolecular etherification reaction; this process would complete the assembly of the polycyclic framework of brevetoxin B and would unquestionably be aided by the *cis* carbon–carbon double bond (*vide supra*). Excision of the superfluous ethylthio grouping from the cyclization product and a few straightforward manipulations would then complete the total synthesis. As previously discussed, the *cis* double bond in **85** provides a convenient opportunity for significant molecular simplification. Tricyclic aldehyde **86** and heptacyclic phosphonium salt **87** can thus be defined as potential precursors to **85**. The reliable and usually stereoselective Wittig reaction would be employed to accomplish the union of compounds **86** and **87** (Scheme 17a).

Tricyclic aldehyde **86** is closely related to compound **77** (see Scheme 15), a substance whose synthesis has been previously described,³⁵ and, like **77**, can ultimately be traced retrosynthetically to D-mannose (**79**). If one examines the constitution of compound **86** carefully, the homology between pyran ring K and D-mannose (**79**) becomes apparent. It was our hope that D-mannose (**79**) could be molded into ring K by a sequence of controlled modifications and that pyran rings J and I could subsequently be annulated in a stepwise fashion through the application of the effective intramolecular Michael addition (Scheme 2) and 6-*endo* activated hydroxy epoxide cyclization reactions (Scheme 1). As shown in Scheme 17a, retrosynthetic disassembly of ring I furnishes hydroxy epoxide **88** as a plausible precursor. Although the α,β -unsaturated ester moiety in **88** is not present in key intermediate **86**, it was expected to play a commanding role in the construction of ring I. On the basis of model studies, it was predicted that the carbon–carbon double bond adjacent to the oxirane ring in **88** would, by stabilizing the incipient positive charge ensuing from protonation of the epoxide oxygen, guide a 6-*endo* hydroxy epoxide cyclization. After it had served its purpose as a regiocontrolling device, the unsaturated ester grouping would then be cleaved. Through a short sequence of

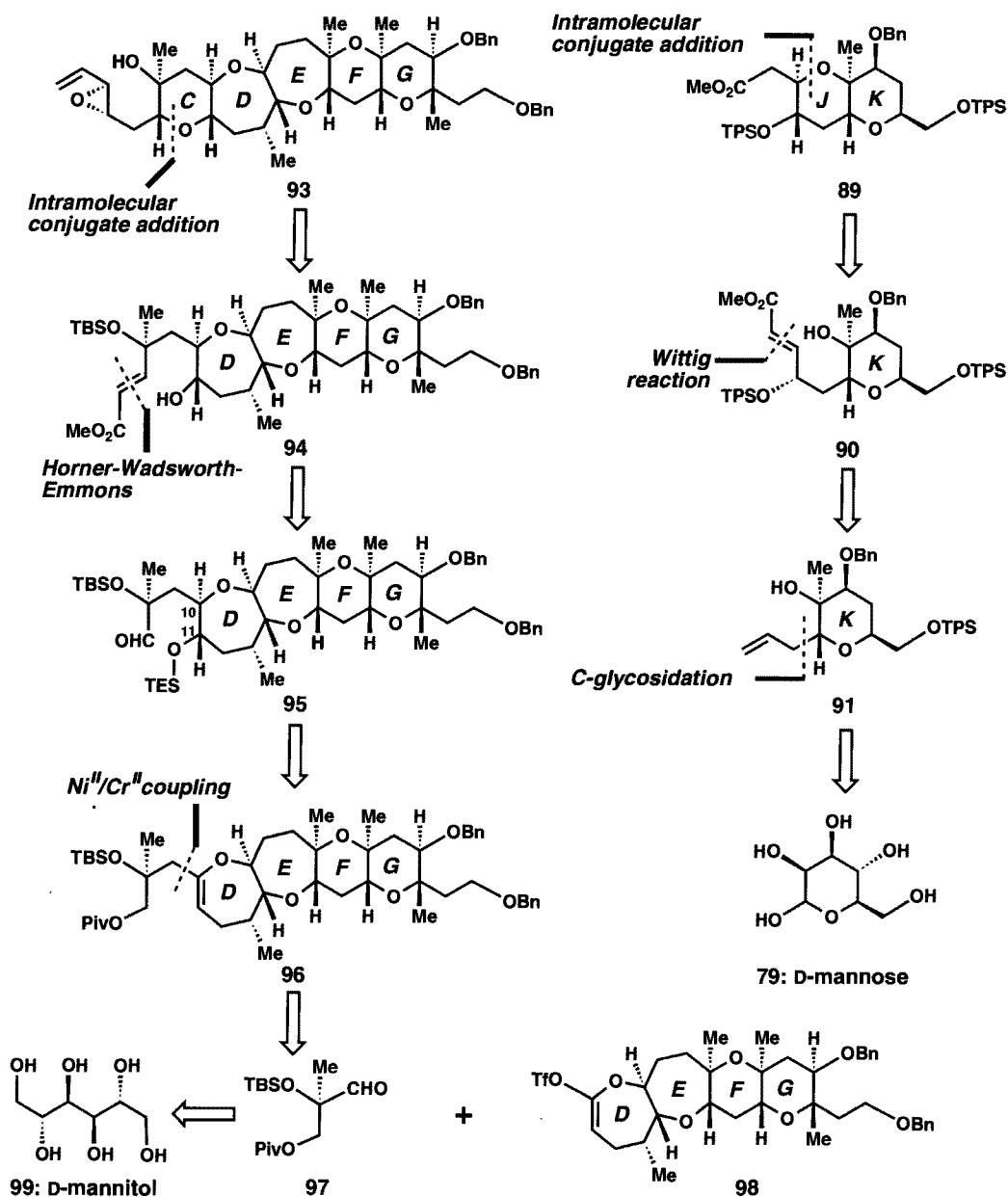


Intramolecular phosphonate-ketone condensation (Homer-Wadsworth-Emmons)

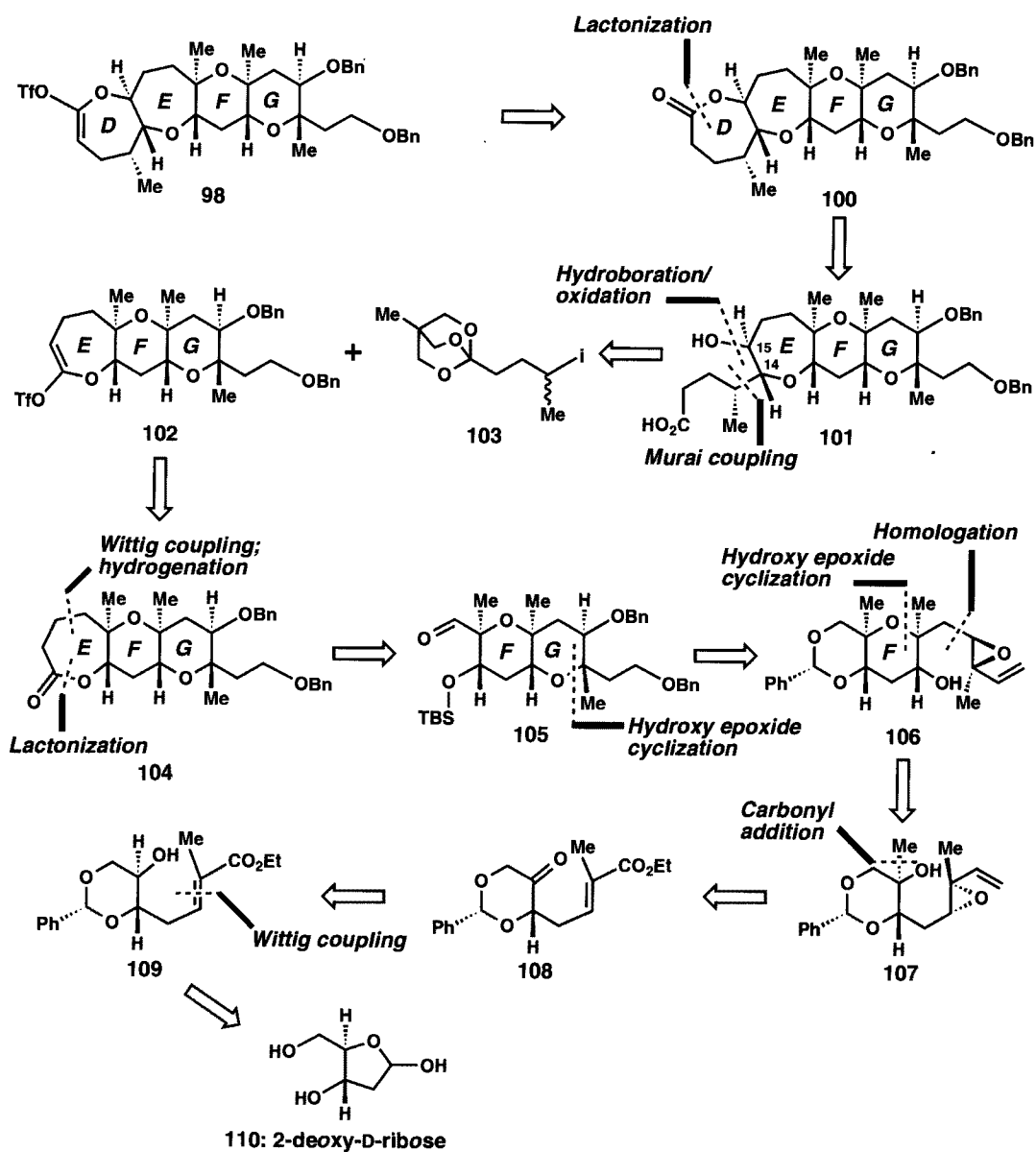




Scheme 17a. Retrosynthetic analysis of brevetoxin B (**1**): the third-generation approach.



Scheme 17b. Retrosynthetic analysis of brevetoxin B (**1**): the third-generation approach (continued).

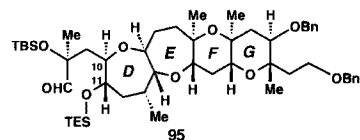
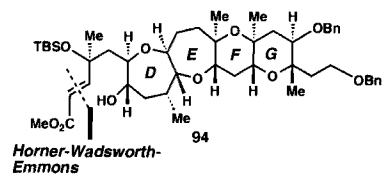
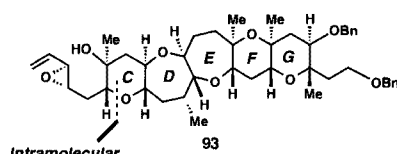
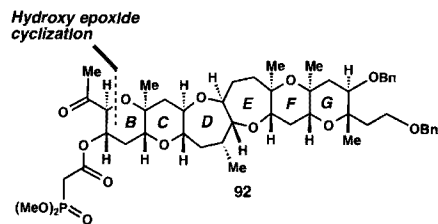
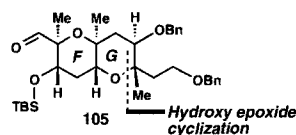
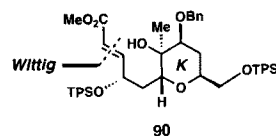
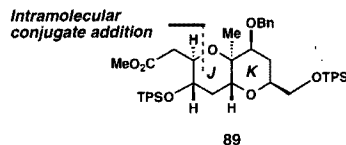


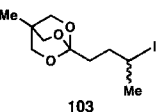
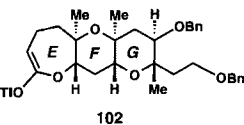
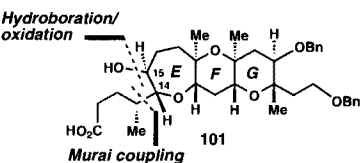
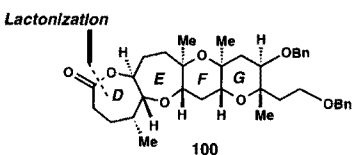
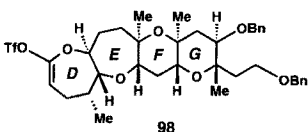
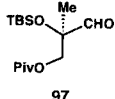
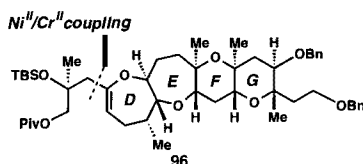
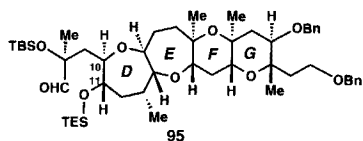
Scheme 17c. Retrosynthetic analysis of brevetoxin B (**1**): the third-generation approach (continued).

manipulations, compound **88** could be fashioned from methyl ester **89**. The relationship between the methoxycarbonyl function and the pyran oxygen of ring J in **89** encouraged the productive possibility revealed by retrosynthetic cleavage of the indicated bond. It was anticipated that the action of a suitable base on **90** would induce an intramolecular conjugate addition reaction (see Scheme 2). Although a stereoisomeric mixture of cyclization products could potentially be formed in such a reaction, compound **89**, in which the methyl acetate side chain is equatorially disposed, was expected to emerge as the major product under thermodynamically-controlled conditions. Compound **91**, the projected precursor of **90**, could, in turn, be derived from D-mannose (**79**) (Scheme 17b).

In contrast to the IJK system **86**, compound **87** (Scheme 17a) poses a much steeper synthetic challenge; it is during the course of the synthesis of **87** that the diabolical bis(oxepane) problem would have to be dealt with. At this phase of the project, we had benefited from a good deal of experience with the bis(oxepane) problem, and this experience provided the foundation for a conservative solution. Starting from FG ring system **105**, it was hoped that rings E, D, C, B, and A could be annulated sequentially and in that order (Scheme 17c).

Keto phosphonate ester **92**, revealed by retrosynthetic disassembly of ring A in **87**, could conceivably participate in an intramolecular Horner–Wadsworth–Emmons (HWE) reaction³⁶ on treatment with a suitable base (Scheme 17a). If successful, this reaction would accomplish the annulation of the A-ring of brevetoxin B. Deoxygenation of the A-ring lactone and a sequence of conventional functional group manipulations would then complete the synthesis of **87**. Compound **92** can be dismantled in a productive fashion by cleavage of the indicated C–O bond. In the synthetic direction, a 6-*endo* activated hydroxy epoxide cyclization of **93** could accomplish the construction of pyran ring B. Manipulation of the substituents attached to the newly formed ring could then furnish compound **92**, the substrate for the A-ring forming HWE reaction. Retrosynthetic disassembly of the C-ring in compound **93** in the manner illustrated reveals α,β -unsaturated hydroxy ester **94** as a potential precursor (Scheme 17b). In the context of **94**, the free secondary hydroxyl group attached to ring D and the electrophilic β -carbon of the unsaturated ester moiety are in proximity. In such a favorable setting, the alkoxide ion resulting from deprotonation of the hydroxyl group in **94** would be expected to take part in a conjugate addition reaction to give pyran ring C. Under equilibrating conditions, this base-induced intramolecular conjugate addition reaction would be expected to afford the desired, more stable C-ring pyran diastereoisomer as the major product. Compound **94**, the requisite substrate for the Michael addition can be traced, in a straightforward manner, to aldehyde **95**. It seemed reasonable to expect that homologation of the aldehyde function in **95** through a *trans*-selective Wittig reaction would, after cleavage of the triethylsilyl ether, afford compound **94**.





Continuing with the retrosynthetic analysis, we still face, in **95**, a rather difficult synthetic problem. Compound **95** possesses a stereochemically and architecturally complex tetraoxacyclic framework consisting of two oxepane and two tetrahydropyran rings. It was projected that compound **95** could be derived from compound **96**. Although this retrosynthetic maneuver does not accomplish appreciable structural simplification, it does reduce, to some extent, the magnitude of the stereochemical problem. In the synthetic direction, a regio- and diastereoselective hydroboration of the enol ether moiety in **96**, followed by oxidative workup, could accomplish the introduction of the adjacent C-10 and C-11 stereocenters in compound **95**. A straightforward sequence of functional group manipulations would then complete the path from **96** to **95** (Scheme 17b).

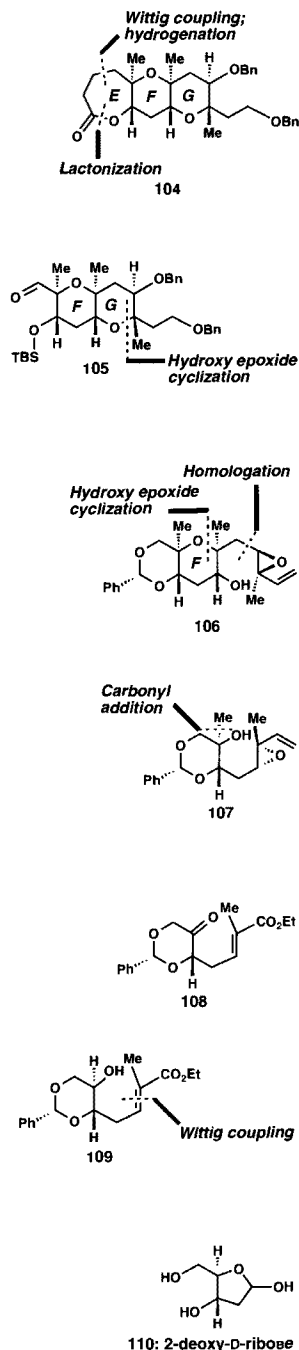
During the course of our work, it was found that enol triflates derived from lactones can be coupled smoothly with aldehydes in the presence of chromium(II) chloride and a catalytic amount of nickel(II) chloride in DMF. Compound **96** can thus be traced to intermediates **97** and **98** by cleavage of the indicated C–C bond. Although the immediate product of a $\text{Ni}^{\text{II}}/\text{Cr}^{\text{II}}$ -mediated coupling of **97** and **98** would contain a superfluous secondary allylic hydroxyl group, compound **96** could be formed, in principle, after a simple Barton deoxygenation sequence. While chiral building block **97** could conceivably be derived from commercially available D-mannitol (**99**), enol triflate **98** could be fashioned in short order from tetracyclic lactone **100** (Scheme 17c). In the context of **100**, ring D is in the form of a lactone which can be conveniently dismantled retrosynthetically to give hydroxy acid **101**. In the forward sense, conversion of the carboxyl function in **101** to a competent acylating agent could be attended by an intramolecular nucleophilic attack by the free hydroxyl attached to ring E; the desired D-ring lactone would then form after collapse of the tetrahedral intermediate. Alternatively, lactone ring formation could occur by the attack of the free hydroxyl group upon a transient and highly electrophilic acylium ion.

The E-ring substituents in **101**, which permit the annulation of ring D, can be removed retrosynthetically to give compounds **102** and **103** as potential precursors. On the basis of Murai's procedure,³⁷ it was anticipated that the carbon side chain attached to oxepane ring E in **101** could be introduced in one step by coupling the higher order organocuprate reagent derived from **103** with enol triflate **102**. The substituted dihydrooxepane thus formed (see **146**, Scheme 25) could then be subjected to a regio- and diastereoselective hydroboration/oxidation sequence. The hydroboration/oxidation of **146**, the equivalent of an anti-Markovnikov hydration of the enol ether, would accomplish the introduction of the adjacent C-14 and C-15 stereogenic centers in **101**. The conspicuous ortho ester function in compound **103** serves an important purpose; this trioxabicyclo[2.2.2]octane group is a useful protecting group for the carbonyl of a carboxyl group and is stable to both basic and nucleophilic reagents.³⁸ At some stage after the Murai coupling of

compounds **102** and **103**, the ortho ester function can be converted to an ester with mild aqueous acid and thence to the requisite carboxyl group with aqueous base.

As we have previously witnessed, enol triflate **102** can be traced to the corresponding lactone (see **104**). In the synthetic direction, enolization of the E-ring lactone in **104** with a strong, non-nucleophilic base, followed by trapping of the lactone enolate oxygen with *N*-phenyltrifluoromethanesulfonimide (PhNTf₂), could give enol triflate **102**. In principle, compound **104** could be derived from FG bicyclic ring system **105** with intermolecular Wittig and lactonization reactions as key synthetic operations. Bis(tetrahydropyran) **105** possesses six stereocenters, and its constitution would seem to lend itself to the powerful 6-*endo* activated hydroxy epoxide cyclization strategy. Although a stereocontrolled synthesis of the FG substructure of brevetoxin B starting from geraniol (**78**) had been achieved,³⁴ a more efficient second-generation synthesis of the FG system from 2-deoxy-D-ribose (**110**) was subsequently developed.³⁹ This second-generation approach to the FG framework is the pathway of choice, and its key features are illustrated in Scheme 17c. Thus, retrosynthetic simplification of **105** as indicated reveals epoxy alcohol **106** as a plausible precursor. On the basis of numerous model experiments, much confidence was invested in the proposition that protonation of the epoxide oxygen in **106** would elicit a regioselective and stereospecific 6-*endo* ring closure to give the desired pyran ring G. Compound **106** can be dismantled in a similar fashion, furnishing epoxy alcohol **107** as a viable precursor. A chemo- and diastereoselective carbonyl addition reaction and standard manipulations could be used to fashion compound **107** from ketone **108**, a substance that can ultimately be traced retrosynthetically to enantiomerically pure 2-deoxy-D-ribose (**110**) (see **108** → **109** → **110**, Scheme 17c).

The first two campaigns (see Schemes 15 and 16) could not overcome the difficulties inherent in the synthesis of the bis(oxepane) region of brevetoxin B. Nonetheless, the bis(oxepane) problem stimulated the development of several novel oxepane-forming methods that are, in many contexts, very effective (see Schemes 5–13). In the sections that follow, the application of the third-generation strategy outlined above (Schemes 17a–c) to the first total synthesis of brevetoxin B (**1**) is described. This doubly convergent approach reduces the synthetic problem to three readily available and enantiomerically pure building blocks, D-mannose (**79**), D-mannitol (**99**), and 2-deoxy-D-ribose (**110**). Although the third-generation path to brevetoxin B features several of the oxacycle-forming strategies already described, the decision was made to utilize reliable lactonization methodology to accomplish the construction of the contiguous oxepane rings in compound **1**.

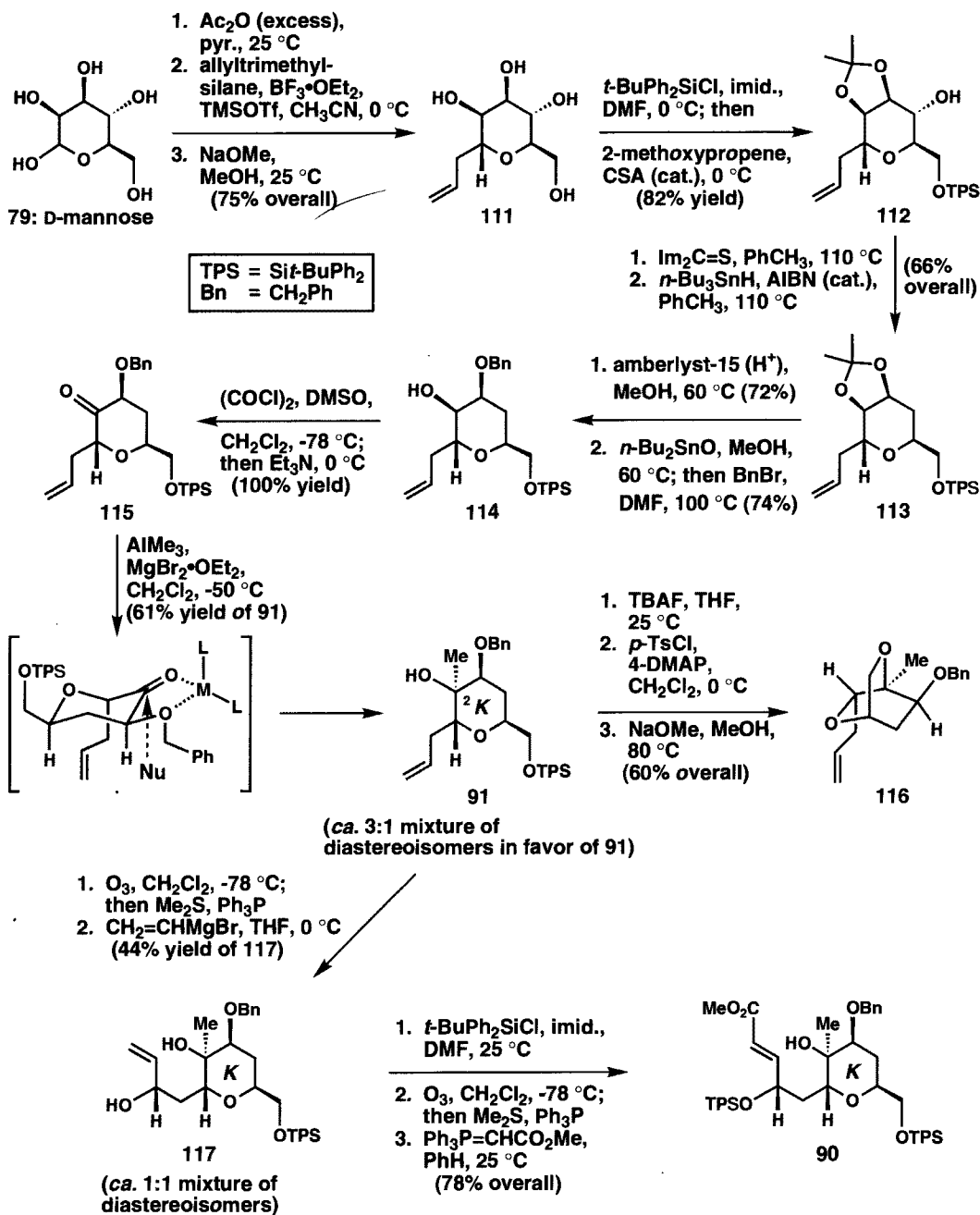


37.3 Total Synthesis

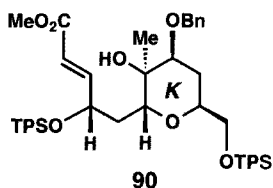
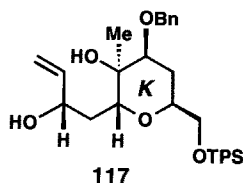
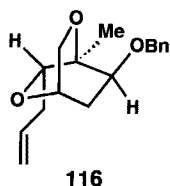
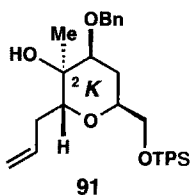
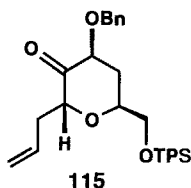
37.3.1 Synthesis of the IJK Framework 86

Our enantiospecific synthesis of IJK aldehyde **86** commences with D-mannose (**79**) (see Scheme 18). Peracetylation of **79** under standard conditions affords the corresponding pentaacetate. Of all the acetoxy functions in D-mannose pentaacetate, the one attached to the anomeric position is particularly susceptible toward displacement. For example, in the presence of boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{OEt}_2$), trimethylsilyl triflate (TMSOTf), and allyltrimethylsilane, the anomeric acetoxy group is selectively replaced with an allyl substituent. It is presumed that the action of a Lewis acid on D-mannose pentaacetate induces the formation of a highly electrophilic acetoxonium ion, which subsequently reacts in a diastereoselective fashion with allyltrimethylsilane to give the desired *α*-C-allylated glycoside (*α*:*β* ca. 7:1).⁴⁰ Solvolytic cleavage of the four remaining acetate esters with sodium methoxide in methanol then furnishes tetraol **111** in 75% overall yield from **79**. After selective silylation of the primary hydroxyl group in **111**, it is possible to accomplish, *in situ*, the simultaneous protection of the two hydroxyl groups residing on the same side of the pyran ring in the form of an acetonide (isopropylidene ketal). Thus, addition of 2-methoxypropene and CSA directly to the silylation reaction mixture results in the formation of compound **112** in 82% overall yield from **111**.

It is important to note, at this juncture, that pyran **112** is destined to become ring K of brevetoxin B (**1**). The free hydroxyl group affixed to the 4-position (carbohydrate numbering) in **112** is not expressed in the natural product and must, therefore, be removed. To this end, reaction of **112** with 1,1'-thiocarbonyldiimidazole in refluxing toluene furnishes a thioimidazolidine which can subsequently be reduced to **113** with tri-*n*-butyltin hydride and a catalytic amount of AIBN (66% overall yield). Exposure of **113** to amberlyst-15 (H^+) in methanol at 60 °C brings about the solvolysis of the acetonide protecting group, affording a 1,2-*cis* diol which reacts smoothly with di-*n*-butyltin oxide to give the corresponding di-*n*-butylstannylene ketal. On the basis of Nashed's protocol,⁴¹ it was anticipated that the stannylene ketal oxygen attached to C-3 (carbohydrate numbering) could be benzylated regioselectively. To accomplish this important transformation, it is first necessary to replace the original solvent, methanol, with the dipolar aprotic solvent, dimethylformamide (DMF). The desired monobenylation can then be accomplished on treatment of the stannylene ketal in DMF at 100 °C with benzyl bromide (74% yield). With the necessary differentiation accomplished, compound **114** can be oxidized, in quantitative yield, to the corresponding ketone (**115**) by application of the Swern procedure. It was our hope that compound **115** would serve as a substrate for a carbonyl addition reaction and permit the



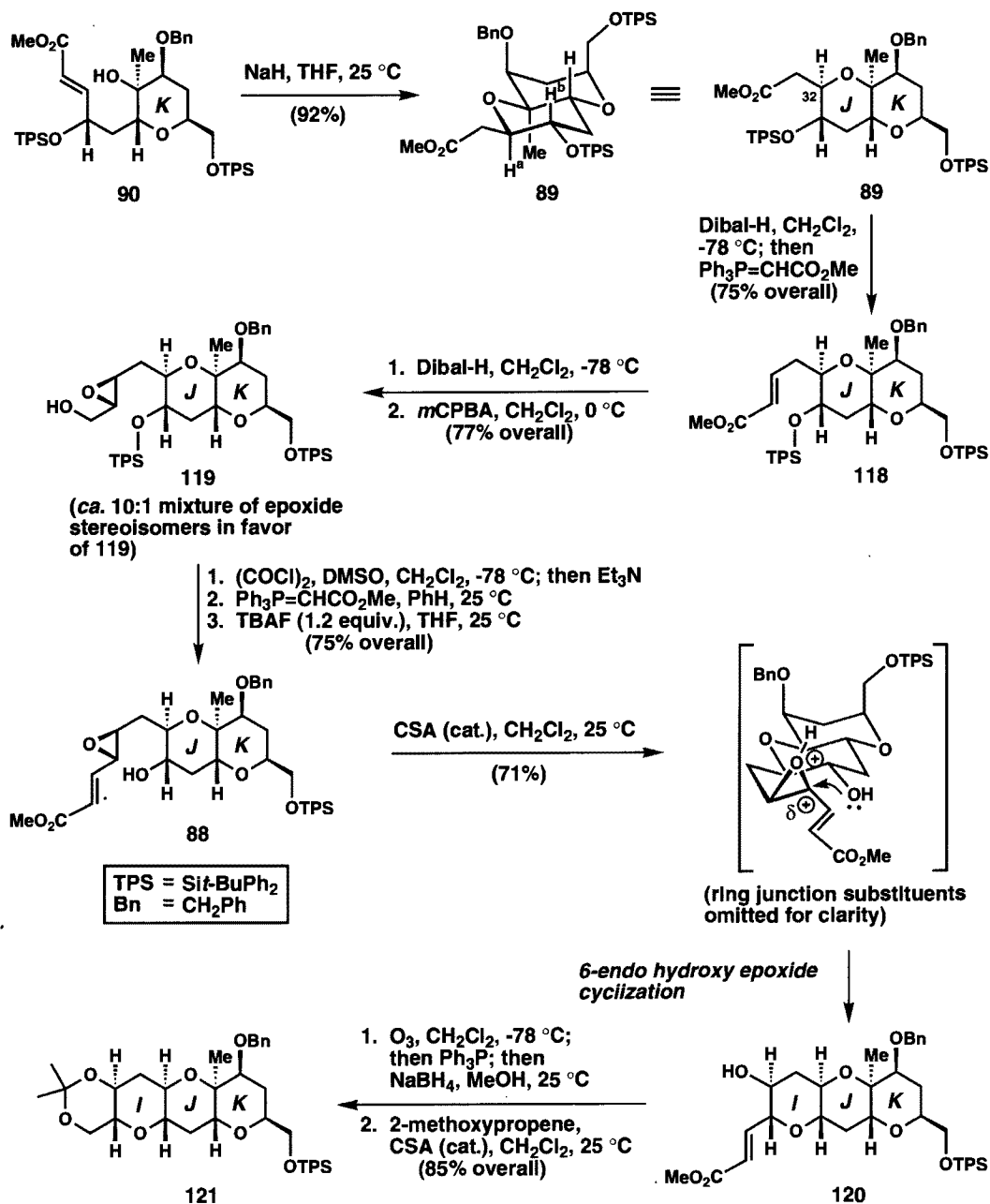
Scheme 18. Construction of the IJK ring system (86): synthesis of intermediate 90.



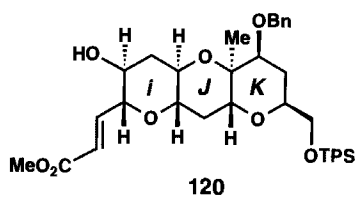
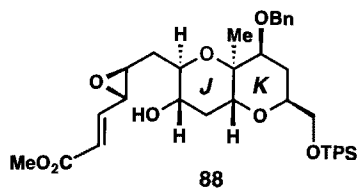
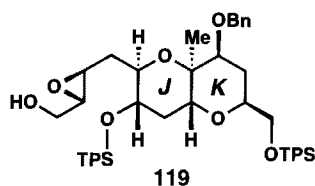
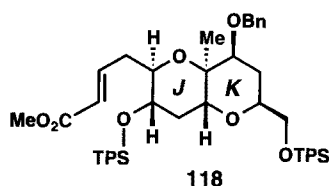
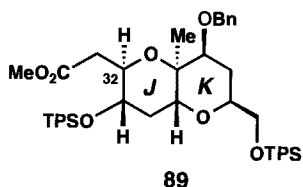
introduction of the fully substituted stereocenter corresponding to C-36 in the natural product. Considering the chiral environment of the keto group, it seemed reasonable to expect that a source of nucleophilic methyl would discriminate between the two diastereotopic faces of the ketone carbonyl. Predicting from which side of the molecule the addition would occur was difficult, however. After some careful experimentation, it was found that when ketone **115** is subjected to the combined action of $\text{MgBr}_2 \cdot \text{OEt}_2$ and trimethylaluminum, it reacts in the expected way, undergoing conversion to a ca. 3:1 mixture of epimeric tertiary alcohols in favor of the desired epimer **91** (81 % total yield). The diastereoselective production of **91** is consistent with a nucleophilic attack upon the α -diastereoface of a chelated ketone carbonyl (see Scheme 18). Interestingly, in the absence of $\text{MgBr}_2 \cdot \text{OEt}_2$, compound **91** is produced with poorer diastereoselectivity (ca. 5:4). At this juncture, the stereochemistry assigned to **91** could be confirmed chemically. For example, compound **91** can be converted to bridged bicycle **116** in three steps by fluoride-induced cleavage of the *tert*-butyldiphenylsilyl (TPS) ether, selective tosylation of the primary hydroxyl, and base-induced cyclic ether formation (see Scheme 18). This successful transformation proves the *syn* relative stereochemical relationship between the tertiary hydroxyl and hydroxymethyl groups in **91**. As expected, the hydroxy tosylate derived from the C-2 epimer of **91** does not cyclize upon treatment with base.

To create a setting favorable for the annulation of ring J, it is obviously necessary to manipulate the allylic side chain. To this end, ozonolytic cleavage of the carbon-carbon double bond in **91** furnishes an aldehyde which reacts smoothly with vinylmagnesium bromide to give an equimolar mixture of diastereomeric allylic alcohols (89 % total yield). Fortunately, these stereoisomeric substances can be separated chromatographically, and the desired epimer, compound **117**, can be obtained in 44 % yield from **91**. The stereochemistry assigned to **117** was confirmed at a subsequent stage by X-ray crystallography. Of the two free hydroxyl groups in **117**, the secondary allylic hydroxyl is the less hindered. It is, therefore, possible to selectively protect the secondary hydroxyl in the form of a *tert*-butyldiphenylsilyl ether. Oxidative cleavage of the terminal carbon-carbon double bond, again using ozone, produces an aldehyde which can be converted to the corresponding α,β -unsaturated ester (**90**) through an (*E*)-stereoselective Wittig reaction with methyl (triphenylphosphoranylidene)acetate (78 % overall yield from **117**).

It will be recalled that one of the key operations in the synthesis of IJK ring system **86** is the intramolecular conjugate addition reaction (see **90** \rightarrow **89**, Scheme 17b) to form ring J. In the context of compound **90**, the electrophilic α,β -unsaturated ester moiety and the potentially nucleophilic tertiary hydroxyl group reside in proximal regions of space, a circumstance that would seem to favor the desired cyclization event (see Scheme 19). Indeed, exposure of a solution of **90** in THF to sodium hydride (1 equiv.) for one hour at 25 °C results in the formation of compound **89** in 92 % yield. In



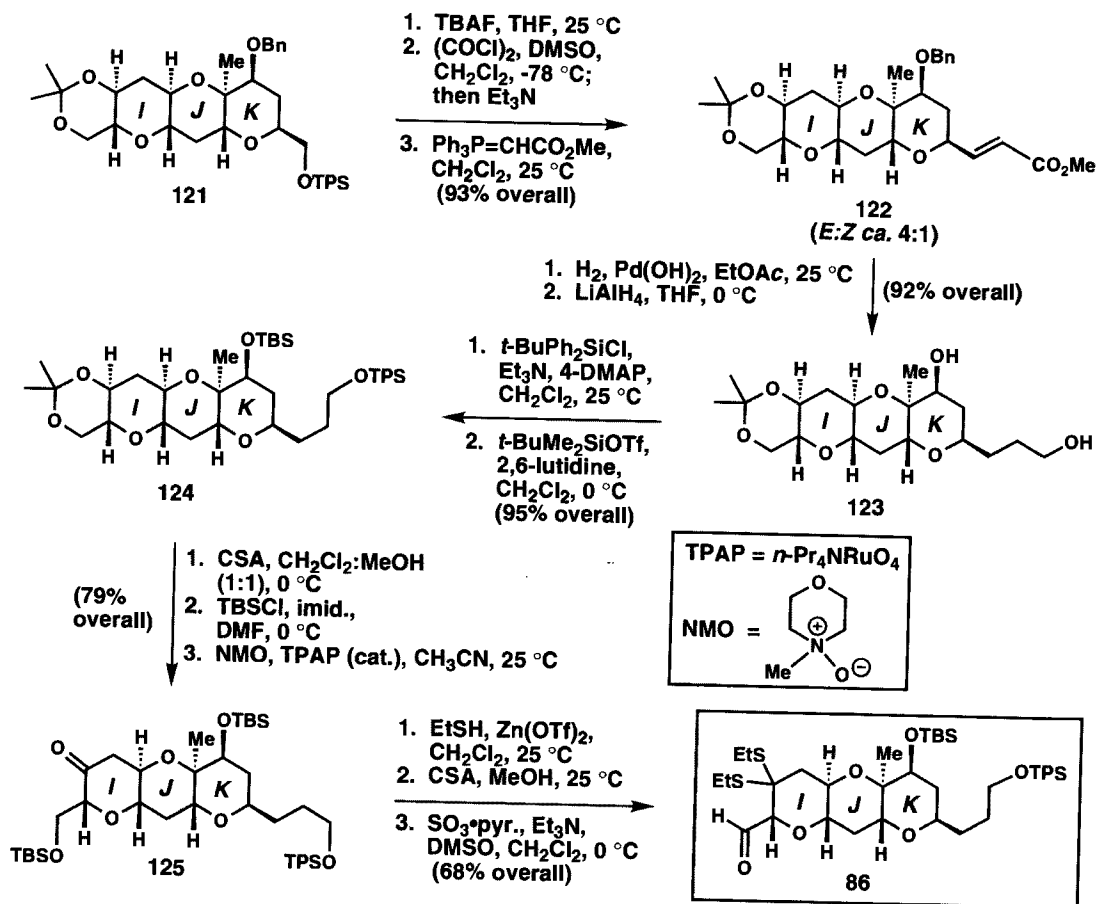
Scheme 19. Construction of the IJK ring system (86): synthesis of intermediate 121.



this reaction, the alkoxide ion generated by deprotonation of the tertiary hydroxyl in **90** initiates ring formation by attacking the electrophilic β -carbon of the unsaturated ester. It is important to note that compound **89**, in which the C-32 side chain is equatorially oriented, is the only stereoisomer observed; even if the undesired C-32 epimer of **89** is formed in this reaction, it equilibrates *in situ* to the desired compound. The observation of a 10.5 Hz H_aH_b coupling constant in the 1H NMR spectrum for **89** is indicative of a *trans* diaxial relationship between these protons, and supports the indicated stereochemistry. A Dreiding model of **89** reveals that the two substituents attached to the newly formed J ring rest comfortably in equatorial positions (see Scheme 19).

The methyl ester side chain in **89** provides a convenient handle for the elaboration of ring I. Although diisobutylaluminum hydride (Dibal-H) is often employed to reduce an ester to the corresponding alcohol, it is possible to partially reduce the methyl ester in **89** to the corresponding aldehyde with Dibal-H (1.5 equiv.) at $-78^\circ C$. It is presumed that coordination of the tetrahedral alkoxide aluminum complex with the J-ring pyran oxygen contributes to the success of this transformation. Now, when the crude aldehyde from the reaction just described is treated with methyl (triphenylphosphoranylidene)acetate, a stereoselective Wittig reaction takes place, affording the (*E*) α,β -unsaturated ester **118** in 75% overall yield from **89**. Reduction of the methyl ester in **118** with 2.2 equivalents of Dibal-H provides an allylic alcohol, the double bond of which can be epoxidized in a surprisingly diastereoselective fashion with *m*CPBA to give a ca. 10:1 mixture of epoxide diastereoisomers in favor of **119** (77% overall yield). Incidentally, Sharpless asymmetric epoxidation⁴² of the allylic alcohol under various conditions gave poor selectivity. Swern oxidation of **119** affords an epoxy aldehyde which can be smoothly homologated through a Wittig reaction (see Scheme 19). Interestingly, when this compound, a bis(silyl ether), is exposed to 1.2 equivalents of TBAF in THF at $25^\circ C$, the apparently more hindered secondary silyl ether can be cleaved with good selectivity (ca. 18:1) to give key intermediate **88** (75% yield from **119**).

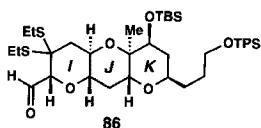
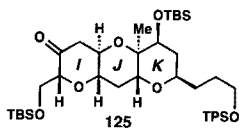
The stage is now set for the annulation of the third and final pyran ring of IJK ring system **86**. Compound **88** is activated for a 6-*endo* hydroxy epoxide cyclization (see Scheme 1). Indeed, if a methylene chloride solution of **88** at $25^\circ C$ is simply treated with a catalytic amount of camphorsulfonic acid (CSA), the desired ring closure takes place in a completely regioselective and stereospecific fashion, giving tricycle **120**, presumably via a chairlike transition state as indicated in Scheme 19 (71% yield). Oxidative cleavage of the carbon-carbon double bond in **120** with ozone affords, after reductive workup, a 1,3-diol which can be protected in the form of an acetonide (see **121**) under standard conditions (85% from **120**). Fluoride-induced cleavage of the *tert*-butyldiphenylsilyl ether, followed sequentially by Swern oxidation and Wittig reactions, furnishes α,β -unsaturated ester **122** (*E*:*Z* ca. 4:1) in 93% overall yield (see Scheme 20). The acquisition of a ca. 4:1 mixture of stereoisomers



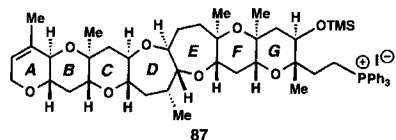
Scheme 20. Synthesis of the IJK ring system (**86**): final stages.

meric unsaturated esters is of no consequence because both isomers converge upon the same intermediate. Thus, hydrogenation of the stereoisomeric unsaturated esters produces a single hydroxy ester; saturation of the carbon–carbon double bond is attended by hydrogenolysis of the benzyl ether. Reduction of the methyl ester function with lithium aluminum hydride then provides diol **123** in 92 % overall yield.

The completion of the synthesis of key intermediate **86** only requires some straightforward manipulations. Differential protection of the two hydroxyl groups in **123** can be easily achieved. Selective silylation of the primary hydroxyl with *tert*-butyldiphenylsilyl chloride provides, after *tert*-butyldimethylsilylation of the remaining secondary hydroxyl, compound **124** (95 % overall yield). Acetone protecting groups can usually be removed under acidic conditions, and the one present in **124** is no exception. Treatment of a solution of **124** in CH₂Cl₂:MeOH (1:1) at 0 °C with CSA

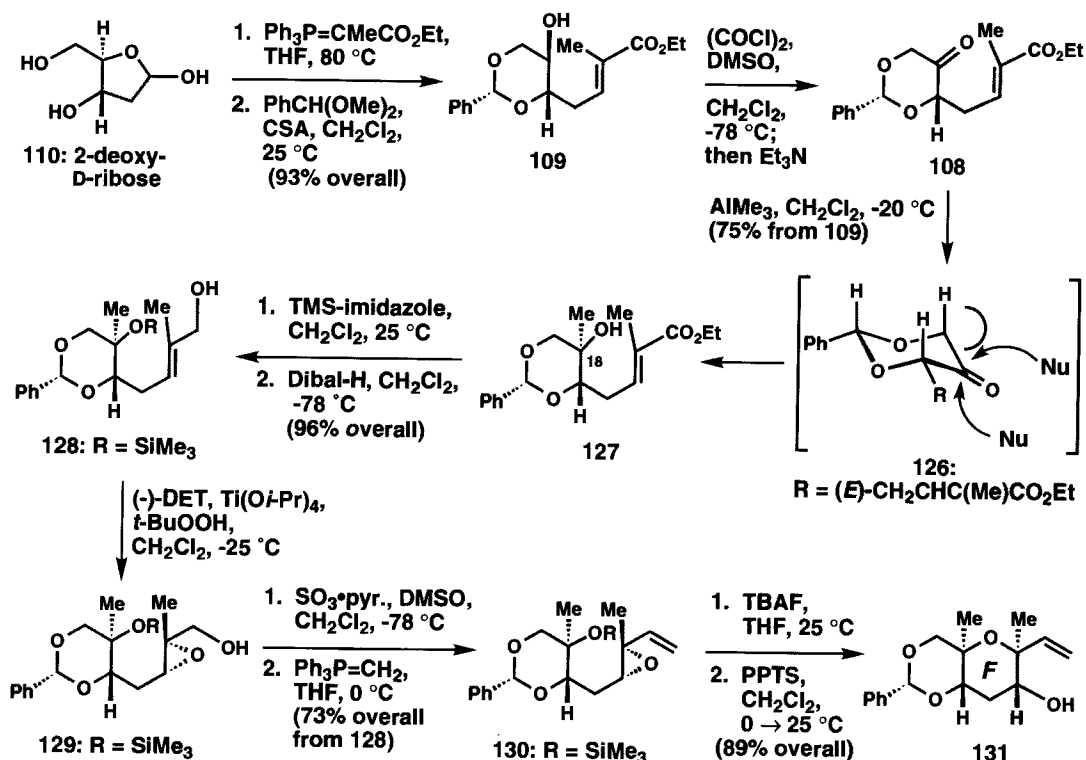


(0.2 equiv.) induces the solvolysis of the acetonide to give a 1,3-diol. Selective silylation of the less hindered primary hydroxyl, followed by oxidation of the remaining secondary alcohol with tetra-*n*-propylammonium perruthenate (TPAP),⁴³ provides ketone **125** in 79 % overall yield from **124**. The I-ring keto group in **125** reacts smoothly with ethanethiol in the presence of zinc triflate to give the corresponding dithioketal. Selective cleavage of the primary *tert*-butyldimethylsilyl ether with methanolic CSA then furnishes the corresponding primary alcohol, which can be converted to key intermediate **86** through oxidation with $\text{SO}_3 \cdot \text{pyridine}$ complex (68 % overall yield from **125**).



37.3.2 Synthesis of the ABCDEFG Framework 87

The path to the complex heptacycle **87** (Scheme 17a) commences with a stereoselective Wittig reaction between 2-deoxy-D-ribose (**110**) and (ethoxycarbonyl ethylidene)triphenylphosphorane (see Scheme 21). This reaction takes advantage of a ring-chain tauto-

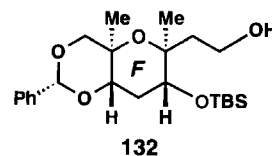
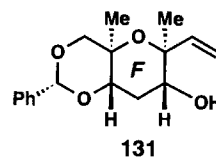


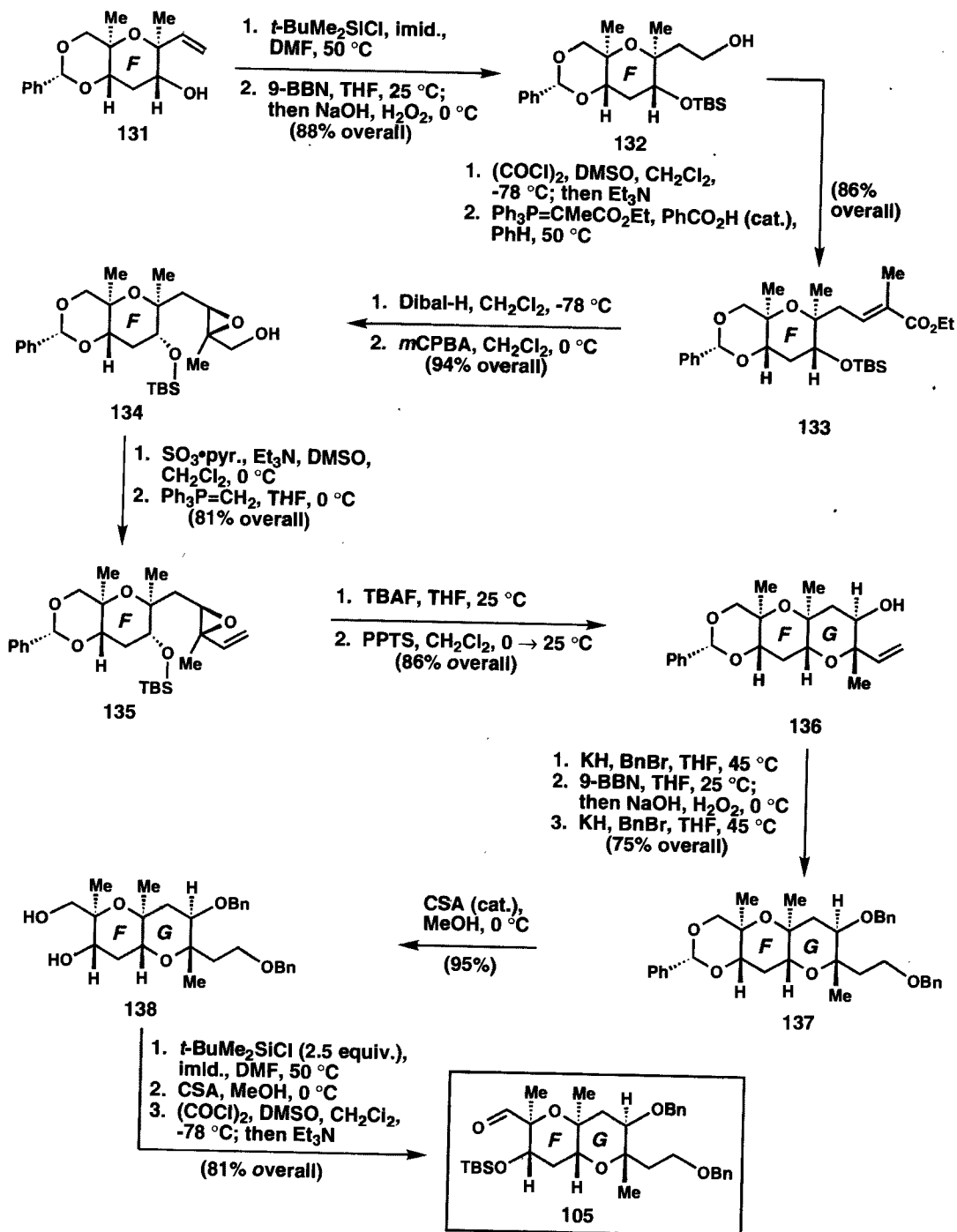
Scheme 21. Construction of the FG ring system (**105**): synthesis of intermediate **131**.

meric equilibrium that naturally exists between lactol **110** and the open-chain aldehyde tautomer.⁴⁴ The terminal aldehydic function of the latter substance is electrophilic, and it obligingly participates in an (*E*)-stereoselective Wittig reaction with the indicated phosphorus ylide to give an α,β -unsaturated ester triol. The presence of three free hydroxyl groups in the product of the above Wittig reaction would, at first glance, appear to present significant differentiation problems. Nonetheless, it is possible to selectively protect the 1,3-diol in the form of a six-membered benzylidene acetal (see **109**) under equilibrating conditions (93 % yield from **110**); relative to the isomeric five-membered benzylidene acetal, the six-membered acetal is thermodynamically more stable. Treatment of ketone **108**, the product of a Swern oxidation of **109**, with trimethylaluminum at -20°C in CH_2Cl_2 accomplishes the formation of tertiary alcohol **127** (75 % overall yield from **109**). This ketone addition reaction deserves a few comments. Although trimethylaluminum could have reacted with the carbonyl of the ethyl ester, it did not; the action of trimethylaluminum on keto ester **108** is thus chemoselective.⁴⁵ It is also important to note that compound **127** is the only diastereoisomer detected. The stereochemical outcome of this reaction is consistent with an axial attack of the nucleophile upon the less hindered, bottom face of the ketone (see **126**). It is likely that an equatorial nucleophilic attack from the top face would be disfavored⁴⁶ due to the presence of the axial hydrogens at positions 2 and 6.

Having accomplished the important task of creating the fully substituted C-18 stereocenter of brevetoxin B (**1**), we could now embark on the construction of pyran ring F. After protection of the tertiary hydroxyl group in **127** as a trimethylsilyl ether with 1-(trimethylsilyl)imidazole, a complete reduction of the ethyl ester with Dibal-H affords allylic alcohol **128** in 96 % overall yield. Sharpless asymmetric epoxidation of the latter compound with the (–)-diethyl tartrate [(–)-DET] chiral ligand proceeds smoothly in the desired and expected way to give an epoxy alcohol (**129**) which can subsequently be converted to the 6-*endo* activated epoxide **130** through straightforward oxidation and Wittig reactions (73 % yield from **128**). Exposure of the epoxy alcohol resulting from fluoride-induced cleavage of the trimethylsilyl ether to the mild acid, pyridinium *para*-toluenesulfonate (PPTS) (0.8 equiv.), in CH_2Cl_2 results in the formation of the desired pyran **131** by a regioselective and stereospecific 6-*endo* hydroxy epoxide cyclization (89 % overall yield from **130**).

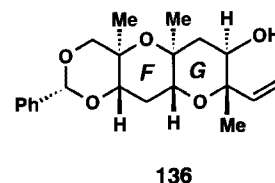
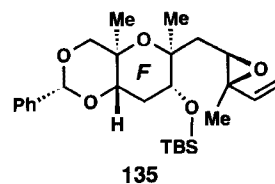
The 6-*endo* activated epoxy alcohol cyclization process was also expected to play a central role in the annulation of pyran ring G of the natural product (see Scheme 22). Silylation of the free secondary hydroxyl group in compound **131** furnishes, after hydroboration/oxidation of the double bond, compound **132**. Swern oxidation of alcohol **132** produces an aldehyde which reacts efficiently with (ethoxycarbonyl ethylidene)triphenylphosphorane in the presence of a catalytic amount of benzoic acid in benzene at 50°C , furnishing





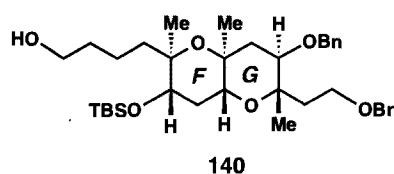
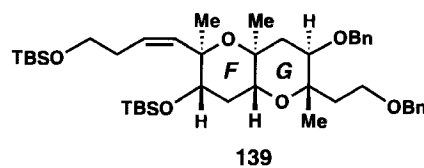
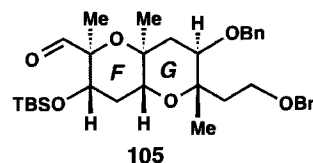
Scheme 22. Synthesis of the FG ring system (**105**): final stages.

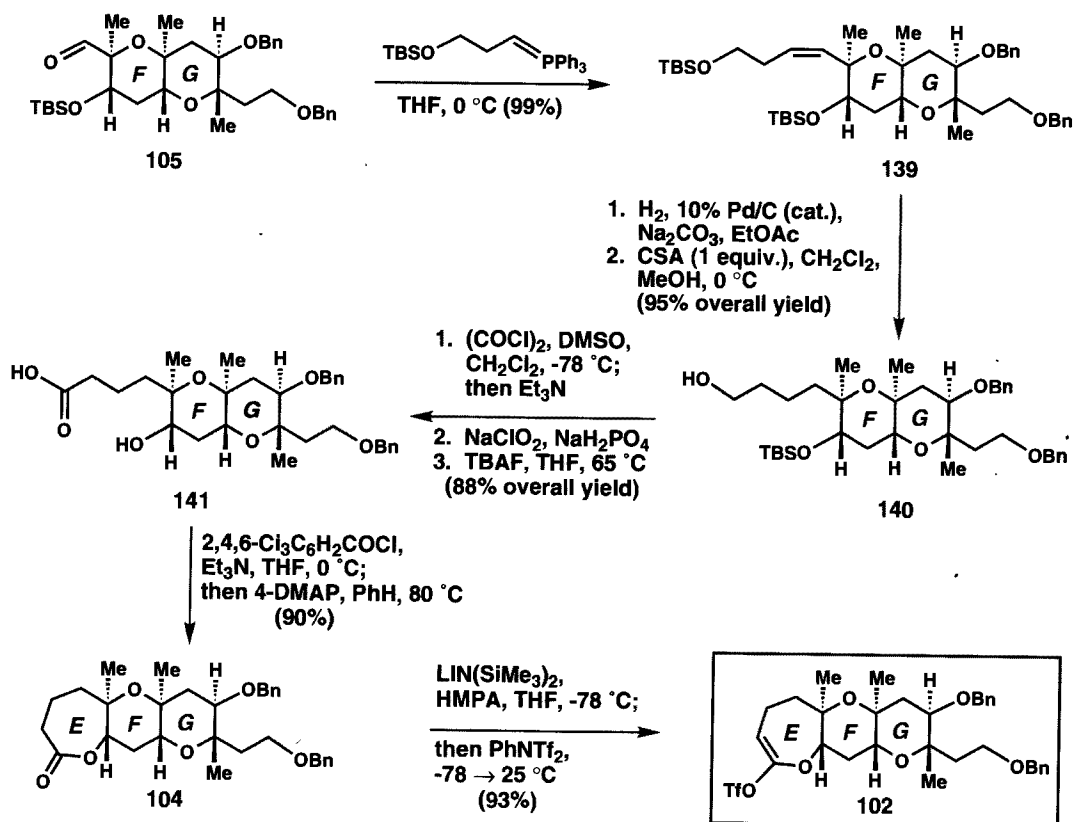
trans α,β -unsaturated ester **133** in 86 % overall yield. Reduction of the ethyl ester in **133** with Dibal-H provides an (*E*) trisubstituted allylic alcohol which can be epoxidized in a highly diastereoselective fashion with *m*CPBA; compound **134** is, in fact, the only epoxide diastereoisomer observed (94 % yield from **133**). This impressive diastereoselectivity is presumably a consequence of a conformationally rigid F-ring, caused by the benzylidene acetal. It is worth noting that epoxidation of the allylic alcohol derived from **133** using the Sharpless procedure [(-)-DET] afforded an unfavorable mixture of the two diastereomeric epoxides. Wittig olefination of the epoxy aldehyde resulting from oxidation of compound **134** with $\text{SO}_3 \cdot \text{pyridine}$ provides 6-*endo* activated epoxide **135** in 81 % overall yield. The epoxy alcohol revealed upon cleavage of the *tert*-butyldimethylsilyl ether in **135** with TBAF undergoes smooth acid-induced cyclization to give the desired bicyclic compound **136** in 86 % overall yield.



With ring G in place, the construction of key intermediate **105** requires only a few functional group manipulations. To this end, benzylation of the free secondary hydroxyl group in **136**, followed sequentially by hydroboration/oxidation and benzylation reactions, affords compound **137** in 75 % overall yield. Acid-induced solvolysis of the benzylidene acetal in **137** in methanol furnishes a diol (**138**) the hydroxy groups of which can be easily differentiated. Although the action of 2.5 equivalents of *tert*-butyldimethylsilyl chloride on compound **138** produces a bis(silyl ether), it was found that the primary TBS ether can be cleaved selectively on treatment with a catalytic amount of CSA in MeOH at 0 °C. Finally, oxidation of the resulting primary alcohol using the Swern procedure furnishes key intermediate **105** (81 % yield from **138**).

According to the third-generation strategy (see Schemes 17a–c), rings E, D, C, B, and A of brevetoxin B are to be annulated sequentially, and in that order, starting from the bicyclic FG system **105**. This linear design relies on the premise that seven-membered ring lactones could serve as progenitors for the oxepane rings of the natural product. The task of constructing the E-ring lactone commences with a (*Z*)-stereoselective Wittig reaction between bicyclic aldehyde **105** and the indicated phosphorus ylide (see Scheme 23). This coupling reaction furnishes compound **139** in nearly quantitative yield, and it accomplishes the introduction of the remaining carbon atoms needed for the annulation of the E-ring. Interestingly, even though the two benzyl ethers in **139** are certainly susceptible to hydrogenolysis, it is possible to selectively hydrogenate the newly formed *cis* C–C double bond in the presence of 10 % Pd/C and a catalytic amount of Na_2CO_3 . Selective acid-induced solvolytic cleavage of the primary TBS ether then furnishes primary alcohol **140** (95 % yield from **139**). Although compound **140** could, in principle, be oxidized to the corresponding carboxylic acid in one step, it proved more reliable to effect this functional group transformation in a stepwise fashion. Thus, Swern oxidation of **140** furnishes an aldehyde which can be oxidized to the desired carboxylic





Scheme 23. Construction of the ABCDEFG ring system (**87**): synthesis of intermediate **102**.

acid by using Pinnick's sodium chlorite (NaClO_2) procedure.⁴⁷ Fluoride-induced cleavage of the silyl ether then furnishes hydroxy acid **141** in 88 % overall yield.

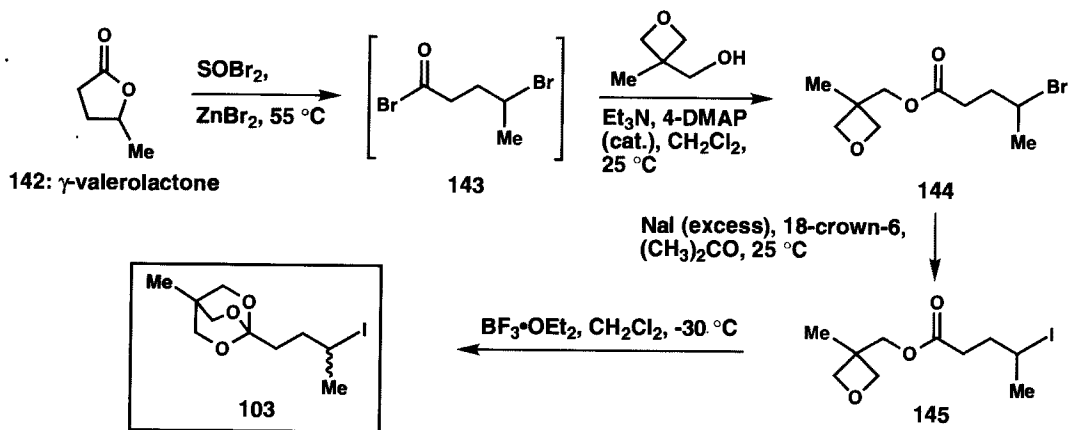
The intramolecular esterification of a carboxylic acid results in the formation of a lactone. To conduct this common-place transformation, the carboxyl function is usually converted into a reactive acylating agent. This carboxyl group activation step is crucial because it enhances the electrophilic character of the carbonyl group, thereby increasing its susceptibility to a nucleophilic attack by a pendant hydroxyl group. Although numerous methods have been developed for the purpose of cyclizing open-chain hydroxy acids,^{25,48} we found that the lactonization of hydroxy acid **141** can be best performed with Yamaguchi's protocol.⁴⁹ In the event, treatment of **141** with 2,4,6-trichlorobenzoyl chloride and triethylamine in THF furnishes a mixed anhydride. When a dilute solution of the latter compound and 4-dimethylaminopyridine (4-DMAP) in benzene is heated to 80 °C, the desired cyclization takes place to give

lactone **104** (90 % yield). Enolization of the newly formed lactone with the strong non-nucleophilic base, lithium bis(trimethylsilyl)amide, affords, after trapping of the lactone enolate oxygen with *N*-phenyltrifluoromethanesulfonimide (PhNTf₂), cyclic ketene acetal triflate **102** (93 % yield).

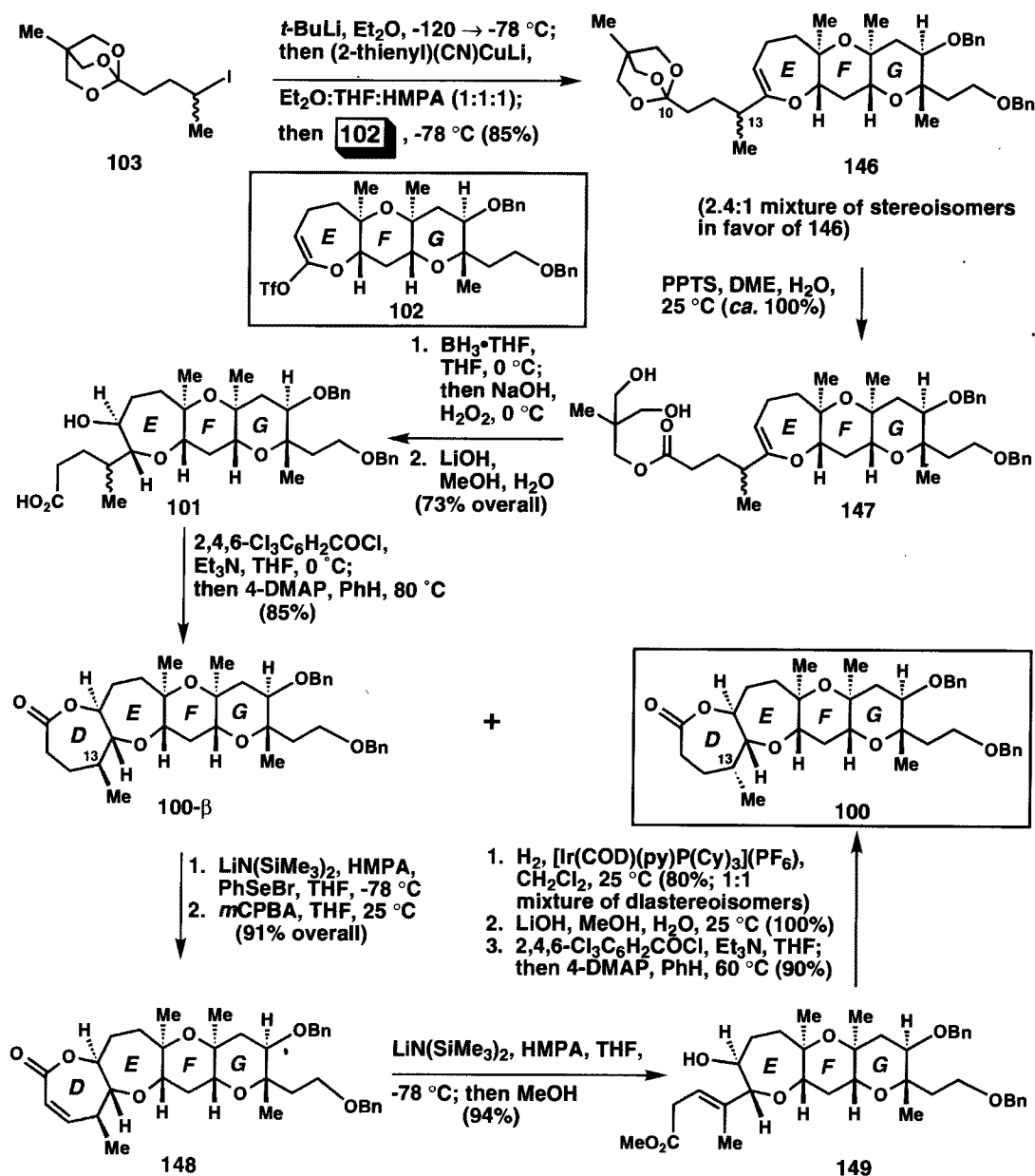
It will be recalled that lactone-derived enol triflate **102** was expected to serve as a substrate for a Murai coupling³⁷ with the mixed cuprate reagent derived from iodo ortho ester **103** (see Scheme 17c). If successful, this C–C bond forming process would accomplish the introduction of the remaining carbon atoms needed for the annulation of the seven-membered D-ring lactone.

Compound **103** possesses a single stereocenter, and it can be conveniently prepared, in racemic form, from γ -valerolactone (**142**) (see Scheme 24). It is presumed that the combined action of thionyl bromide and zinc bromide on **142** results in the formation of acyl bromide **143**; the latter substance, a highly reactive acylating agent, then reacts with 3-methyl-3-hydroxymethyl oxetane in the expected way to give oxetane ester **144**. Under these conditions, the Lewis acid induced conversion of acyl bromide **143** to a highly reactive acylium ion which is subsequently captured by 3-methyl-3-hydroxymethyl oxetane is also plausible. Compound **145**, the product of a simple Finkelstein exchange reaction, can then be converted to iodo ortho ester **103** upon exposure to BF₃•OEt₂ (70 % yield).⁵⁰

With compounds **102** and **103** in hand, we are now in a position to address the crucial Murai coupling. In the presence of two equivalents of *tert*-butyllithium, iodide **103** participates in a halogen–lithium exchange reaction, and the resulting organolithium is converted to a higher order organocuprate reagent on treatment with lithium thienylcyanocuprate⁵¹ (see Scheme 25). When this mixed cuprate reagent is reacted with cyclic ketene acetal triflate



Scheme 24. Synthesis of iodo ortho ester **103**.



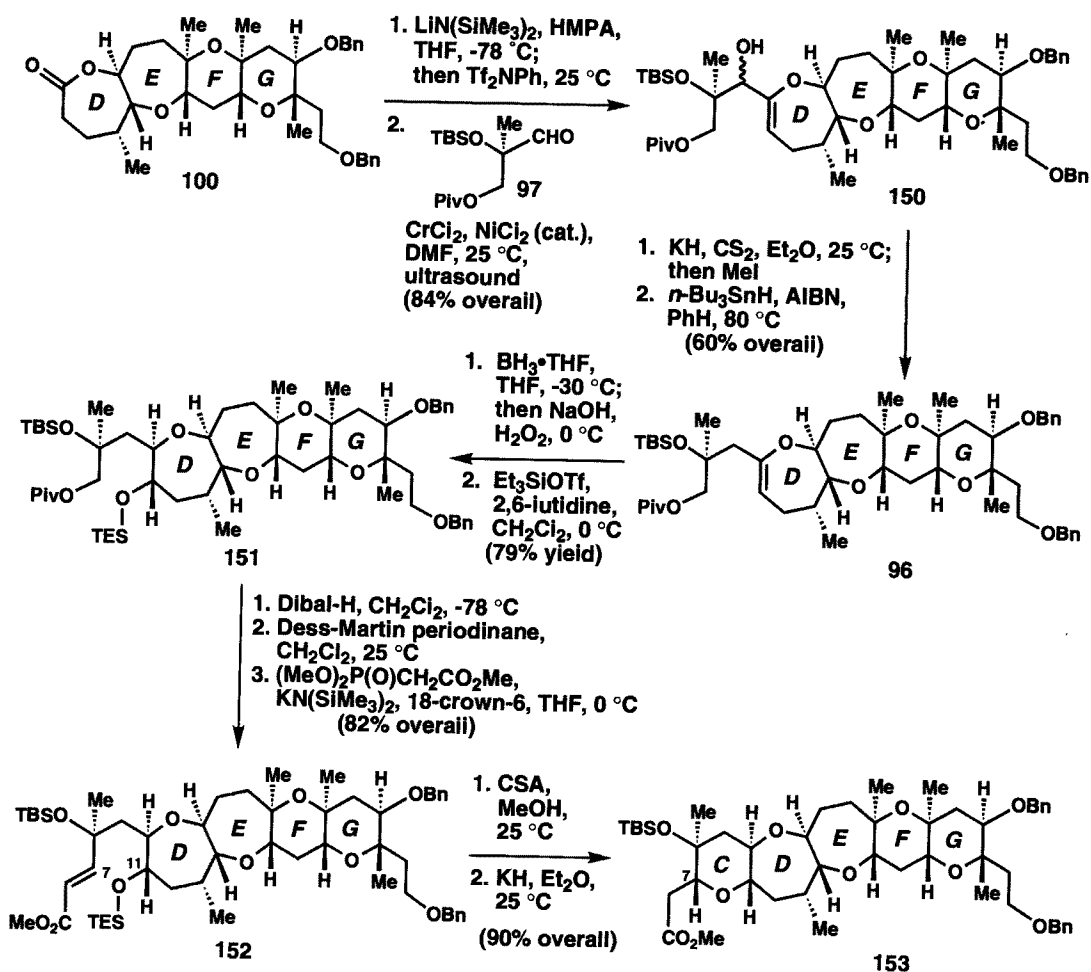
Scheme 25. Construction of the ABCDEFG ring system (87): synthesis of lactone **100**.

102, the desired union takes place, affording **146** as a 2.4:1 mixture of C-13 epimers in favor of the desired stereoisomer (85 % total yield). The observed diastereoselectivity, as modest as it is, was not anticipated, and it should be noted at this point that the desired epimer is produced as the major product provided that the solvent system Et₂O:THF:HMPA (1:1:1) is employed in the coupling reaction. Unfortunately, it was not possible to separate the two diastereoisomers at this stage.

With the side chain comprising carbons 10–13 of the natural product in its proper place, the task of annulating lactone ring D could be addressed. At this stage, our plan called for the hydroboration/oxidation of the E-ring didehydrooxepane double bond in **146**. This oxidative transformation, the equivalent of an anti-Markovnikov hydration of the enol ether, could accomplish the simultaneous introduction of the contiguous C14–C15 stereogenic centers, and it was one with which we had some familiarity. Interestingly, attempts to hydroborate compound **146** with BH₃•THF were attended by reduction of the ortho ester function. It is presumed that hydroboration of the double bond takes place first, followed by a boron-assisted intramolecular reductive cleavage of the proximal ortho ester. To circumvent this problem, ortho ester **146** is converted, through the action of mild aqueous acid, to dihydroxy ester **147** (ca. 100 % yield). Gratifyingly, when the latter compound is exposed to six equivalents of BH₃•THF, the desired hydroboration takes place regio- and diastereoselectively, affording the required secondary alcohol after oxidative workup. Basic hydrolysis (saponification) of the ester function then provides hydroxy acid **101** (73 % overall yield). As expected, lactonization of **101** through the application of the Yamaguchi procedure⁴⁹ provides a 2.4:1 mixture of diastereomeric lactones, epimeric at C-13, in favor of the desired compound **100**; both lactone diastereoisomers could be obtained in pure form after silica gel chromatography.

In an effort to make productive use of the undesired C-13 epimer, **100-β**, a process was developed to convert it into the desired isomer **100**. To this end, reaction of the lactone enolate derived from **100-β** with phenylselenenyl bromide produces an α -selenated lactone which can subsequently be converted to α,β -unsaturated lactone **148** through oxidative *syn* elimination (91 % overall yield). Interestingly, when **148** is treated sequentially with lithium bis(trimethylsilyl)amide and methanol, the double bond of the unsaturated lactone is shifted, the lactone ring is cleaved, and β,γ -unsaturated methyl ester alcohol **149** is formed in 94 % yield. In light of the constitution of compound **149**, we were hopeful that a hydroxyl-directed hydrogenation⁵² of the trisubstituted double bond might proceed diastereoselectively in the desired direction. In the event, however, hydrogenation of **149** in the presence of [Ir(COD)(py)P(Cy)₃](PF₆)⁵³ produces an equimolar mixture of C-13 epimers in 80 % yield. Sequential methyl ester saponification and lactonization reactions then furnish a separable 1:1 mixture of lactones **100** and **100-β** (72 % overall yield from **149**).

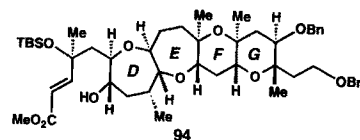
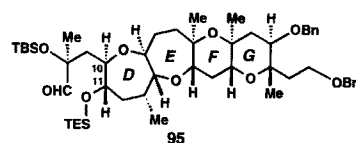
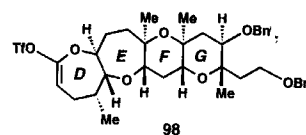
A rather advanced stage in the synthesis of the ABCDEFG fragment **87** has been reached. Having surmounted the barrier posed by the seven-membered rings in brevetoxin B, we were faced with the task of devising some means of annulating pyran rings C, B, and A. At this phase of the project, we were mindful of the important work of Nozaki⁵⁴ and Kishi⁵⁵ that demonstrated the facility with which ketone-derived enol triflates can be coupled with aldehydes in the presence of chromium(II) chloride and nickel(II) chloride.⁵⁶ On the basis of this precedent, it was projected that lactone-derived enol triflates (cyclic ketene acetal triflates) might also perform well in Ni^{II} / Cr^{II} -mediated coupling reactions with aldehydes. To test the feasibility of this proposition, cyclic acetal ketene triflate **98** (Schemes 17b,c) was prepared by triflation of the enolate oxygen formed on deprotonation of **100** with $\text{LiN}(\text{SiMe}_3)_2$ (see Scheme 26). When a



Scheme 26. Construction of the ABCDEFG ring system (**87**): synthesis of intermediate **153**.

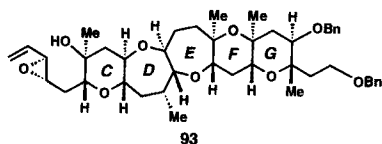
solution of cyclic ketene acetal triflate **98** (1 equiv.) and the aldehyde **97** derived from D-mannitol (6 equiv.) in DMF at 25 °C is sonicated in the presence of CrCl₂ (6 equiv.) and a catalytic amount of NiCl₂, the desired coupling takes place and compound **150** is formed as a mixture of epimers (64 % from **100**). It is of no consequence that compound **150** is produced as a mixture of diastereoisomers because the newly formed hydroxyl group is not expressed in the natural product; it must, furthermore, be removed. To accomplish this objective, Barton's two-stage deoxygenation procedure⁵⁷ was selected. Thus, reaction of alcohol **150** with potassium hydride and carbon disulfide provides, after quenching with methyl iodide, the corresponding xanthate. Exposure of the latter substance to tri-*n*-butyltin hydride and a catalytic amount of AIBN then accomplishes the desired reduction to give compound **96** in 60 % yield. As straightforward as it appears, this two-step reduction sequence is worthy of special comment. When attempts were made to convert alcohol **150** to the corresponding xanthate, it was found that the alkoxide ion formed upon deprotonation of the secondary alcohol initiates a silyl group migration. This event places the congested *tert*-butyldimethylsilyl group on the less hindered oxygen and generates, concomitantly, a tertiary alkoxide. Although favored at equilibrium, the tertiary alkoxide, due to its hindered nature, does not react with carbon disulfide. Furthermore, even though the secondary alkoxide ion is the minor component of the alkoxide equilibrium, it reacts with carbon disulfide in the desired way. It is also noteworthy that the *n*-Bu₃SnH/AIBN-induced C–O bond cleavage is accompanied by migration of the adjacent carbon–carbon double bond, leading to a regioisomeric mixture of enol ethers. Fortunately, Wilkinson's catalyst, [(Ph₃P)₃RhCl], can bring about the isomerization of the undesired exocyclic enol ether to compound **96**, thus increasing the yield to 82 %.

From compound **96**, the construction of ring C of brevetoxin B can be accomplished smoothly as shown in Scheme 26. Regio- and diastereoselective hydroboration/oxidation of the D-ring double bond provides, after triethylsilylation of the newly introduced hydroxyl group, compound **151** in 79 % overall yield. Reductive cleavage of the pivalate ester in **151** with Dibal-H furnishes a primary alcohol which can be oxidized with Dess–Martin periodinane⁵⁸ to aldehyde **95** (see Scheme 17b). Subjection of the latter compound to a HWE reaction with the potassium salt of (MeO)₂P(O)CH₂CO₂Me then furnishes *trans* α,β-unsaturated ester **152** in 82 % overall yield from **151**. On treatment with CSA in methanol at 25 °C, the triethylsilyl ether in **152** is cleaved selectively, affording hydroxy ester **94** (see Scheme 17b) in quantitative yield. In **94**, the secondary hydroxyl group attached to C-11 and the electrophilic β-carbon of the unsaturated ester occupy neighboring regions of space. It is therefore not surprising that compound **94** participates in an intramolecular conjugate addition reaction upon exposure to potassium hydride. Interestingly, if this pyran ring forming reaction is quenched shortly after the addition of potassium hydride, then a



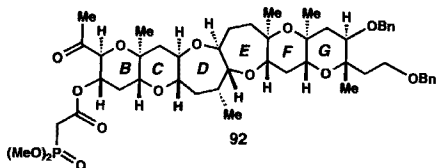
mixture of stereoisomeric cyclization products, epimeric at C-7, is produced. On prolonged reaction time, however, the undesired C-7 epimer undergoes conversion to the desired stereoisomer **153**, presumably through a retro-Michael/Michael process; compound **153** thus emerges as the product of a thermodynamically controlled ring closure.

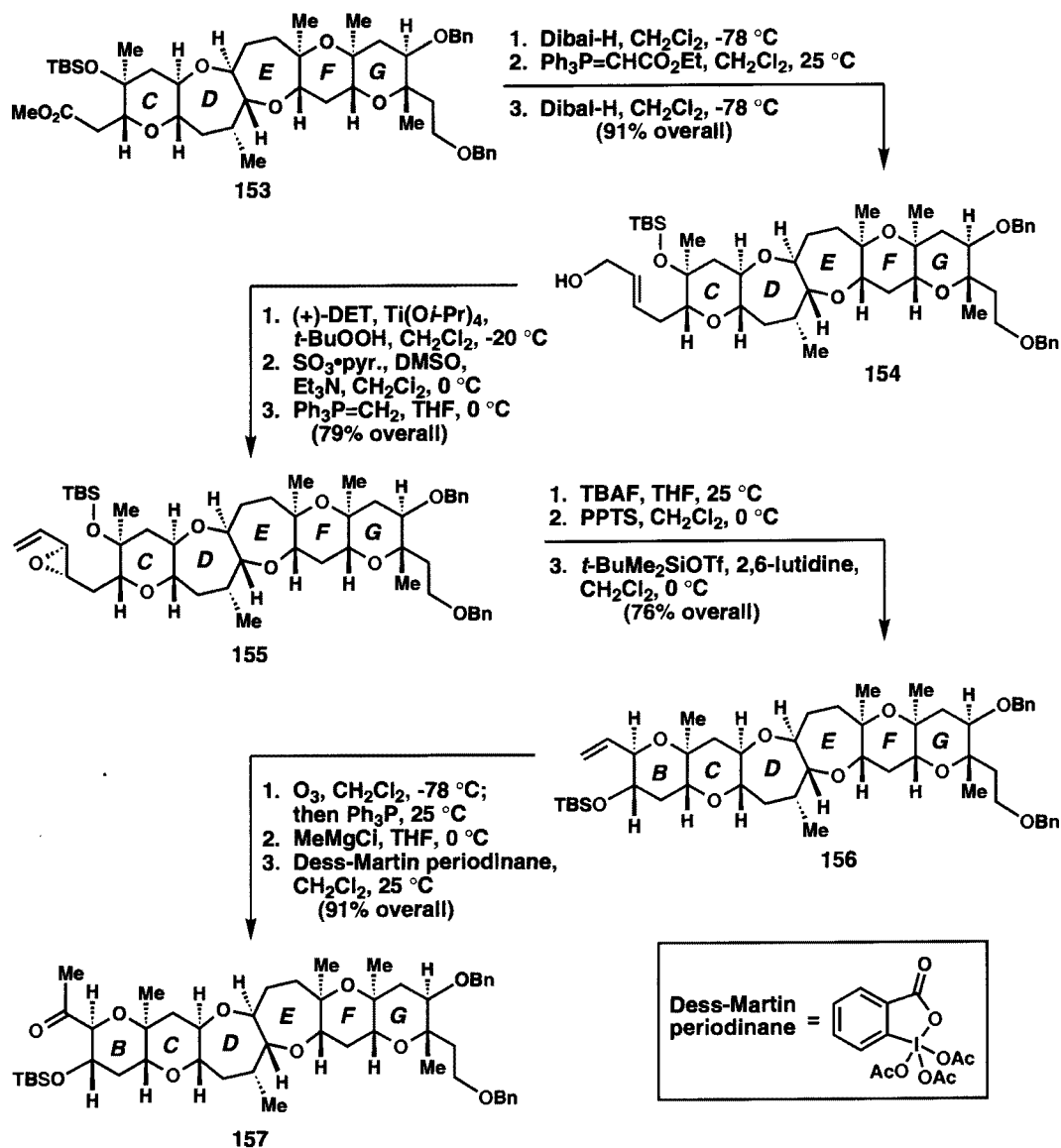
The methyl ester in pentacycle **153**, which played such a crucial role in the formation of the C-ring, provides a convenient handle and an opportunity to accomplish the annulation of pyran ring B. It was our hope that ring B could be formed by the 6-*endo* activated hydroxy epoxide cyclization method. The implementation of this plan commences with a partial reduction of the methyl ester in **153** with Dibal-H (Scheme 27). Wittig reaction of the resulting aldehyde with the indicated stabilized ylide provides an (*E*) α,β -unsaturated ethyl ester which can be reduced to the corresponding primary alcohol **154** with Dibal-H. Sharpless asymmetric epoxidation of **154** with (+)-diethyl tartrate [(+)-DET] as the chiral ligand furnishes, after sequential oxidation and Wittig reactions, 6-*endo* activated epoxide **155** in 79% overall yield. Compound **93** (see Scheme 17b), obtained by fluoride-induced cleavage of the silyl ether in **155**, participates in the desired 6-*endo* cyclization upon treatment with PPTS in CH_2Cl_2 . Silylation of the newly formed secondary hydroxyl group then furnishes compound **156** (76% yield from **155**).



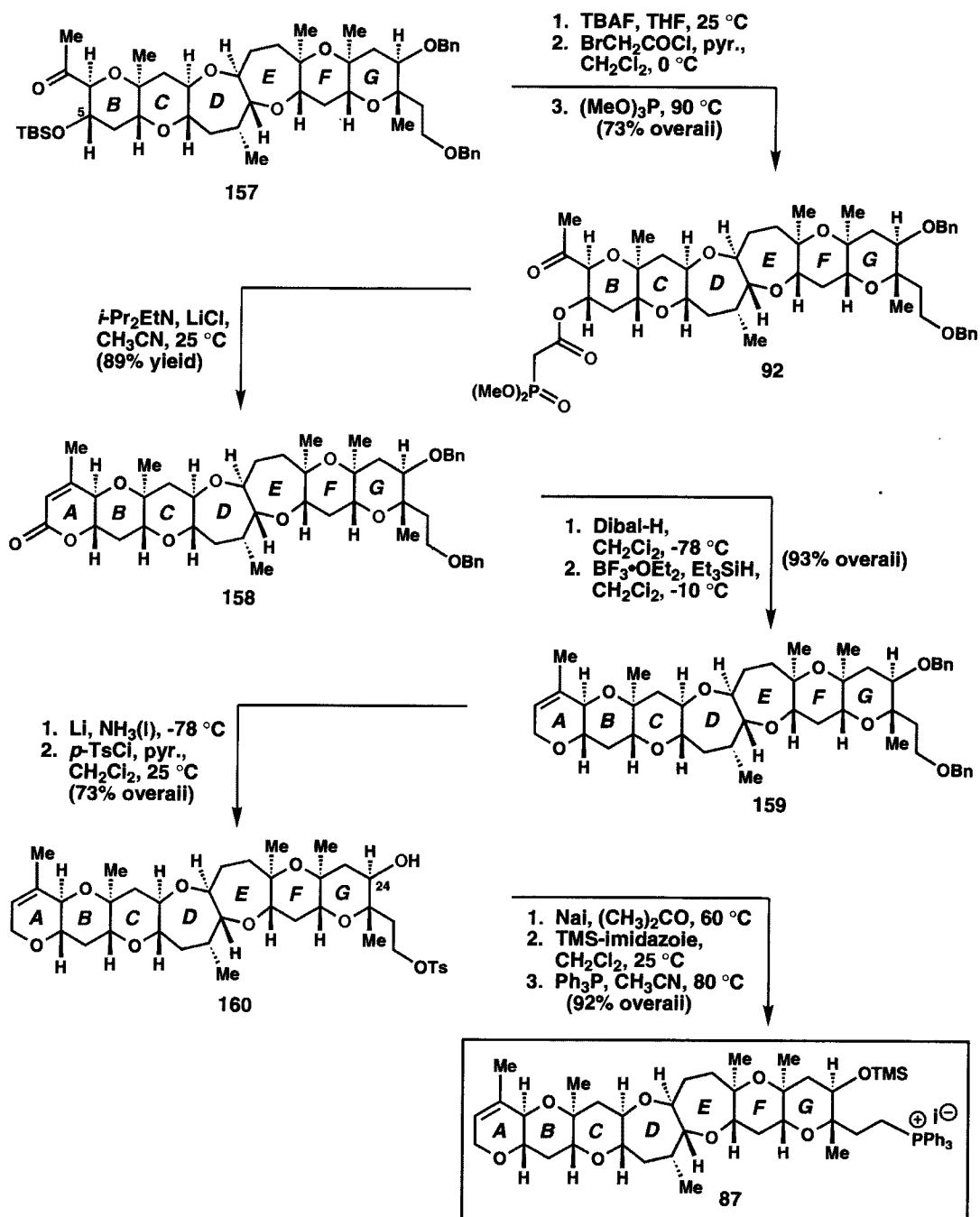
Having served its purpose as a regiocontrolling device, the carbon-carbon double bond in compound **156** must be modified in a manner conducive to the construction of ring A in brevetoxin B. According to the general plan outlined in Scheme 17a, it would be necessary to convert this monosubstituted olefin into a methyl ketone. To this end, oxidative cleavage of the carbon-carbon double bond in **156** with ozone produces an aldehyde which reacts smoothly with methylmagnesium chloride in THF to give a mixture of epimeric secondary alcohols. Oxidation of this mixture with Dess-Martin periodinane⁵⁸ then furnishes methyl ketone **157** in 91% overall yield (Scheme 27).

The construction of ring A and the completion of the synthesis of the ABCDEFG fragment **87** is detailed in Scheme 28. It seemed reasonable to propose that if a suitable phosphonate-containing side chain could be attached to the C-5 oxygen atom, then it might be possible to construct ring A through an intramolecular HWE reaction. Keto phosphonate ester **92** can in fact be elaborated in short order from **157**. Thus, fluoride-induced cleavage of the C-5 silyl ether in **157** affords a secondary alcohol which can be smoothly acylated with bromoacetyl chloride in the presence of pyridine to give a bromoacetate ester. The latter compound, on treatment with trimethyl phosphite, participates in an Arbuzov reaction⁵⁹ and undergoes conversion to the desired phosphonate **92** (73% yield from **157**). In **92**, the enforced proximity of groupings having complementary reactivity creates a very favorable setting for the desired annulation. Indeed, when compound **92** is exposed to lithium chlor-





Scheme 27. Construction of the ABCDEFG ring system (**87**): synthesis of intermediate **157**.



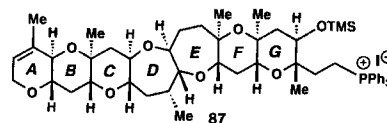
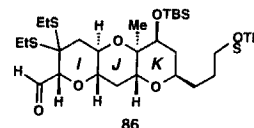
Scheme 28. Construction of the ABCDEFG ring system (**87**): final stages.

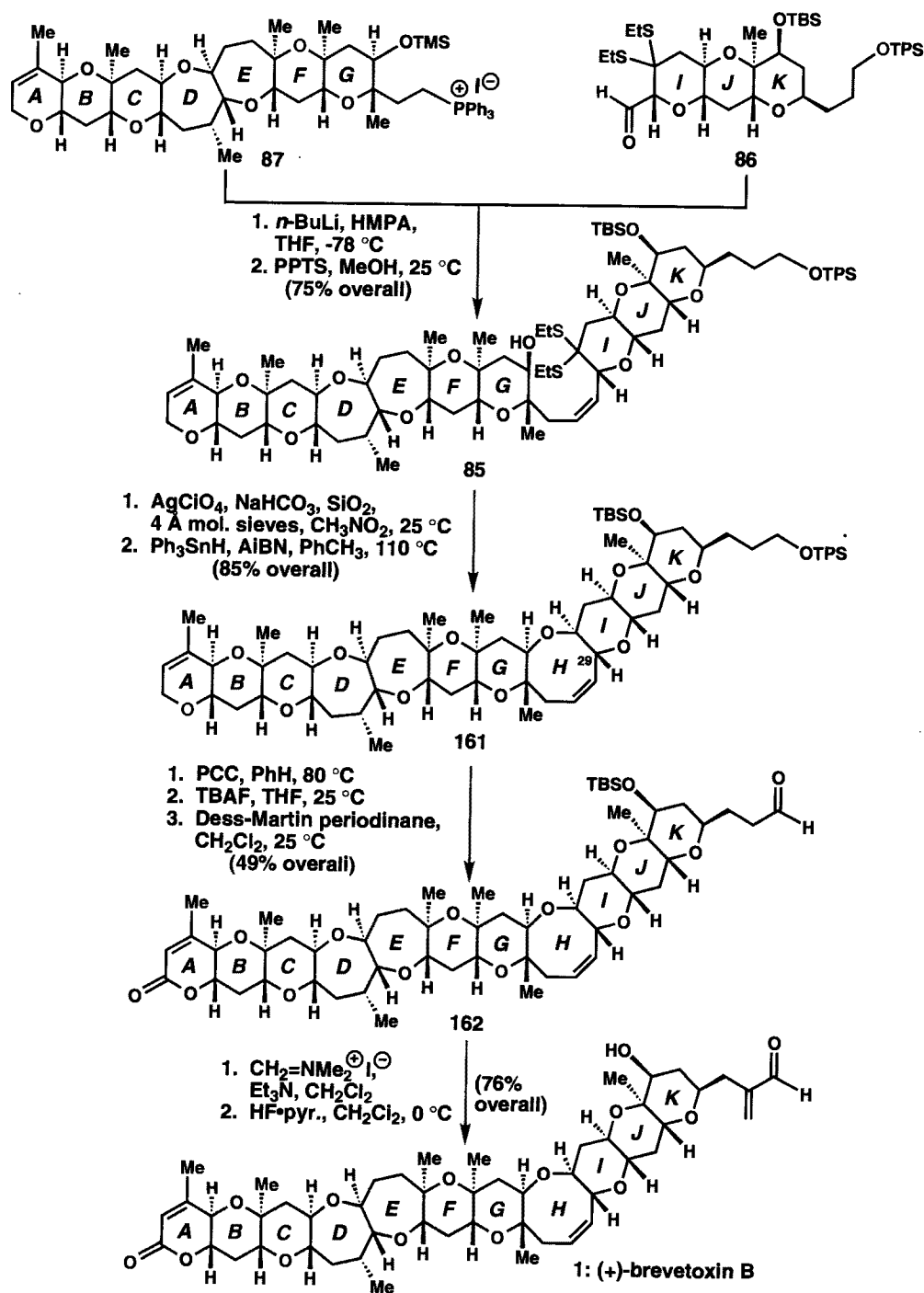
ide and Hünig's base in acetonitrile at 25 °C,⁶⁰ the desired intramolecular HWE reaction proceeds efficiently, affording α,β -unsaturated lactone **158** in 89 % yield.

Although the A-ring lactone carbonyl in compound **158** is also found in the natural product, the electrophilic character of this function interferes with subsequent stages of the synthesis. The decision was thus made to reduce the A-ring lactone to the corresponding ether. To this end, treatment of **158** with Dibal-H provides the corresponding lactol, a compound that undergoes further reduction to **159** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ and triethylsilane. After construction of the polycyclic framework of brevetoxin B, the A-ring lactone carbonyl could then, in principle, be reintroduced through oxidation of the C-1 methylene group. The final stages in the synthesis of key intermediate **87** are rather straightforward (see Scheme 28). When compound **159** is subjected to the action of lithium metal in liquid ammonia at -78°C , the two benzyl ethers are cleaved and a diol is formed. Selective tosylation of the less hindered primary hydroxyl then furnishes hydroxy tosylate **160**, a compound that reacts smoothly with iodide ion to give the corresponding hydroxy iodide. After protection of the free C-24 hydroxyl in the form of a trimethylsilyl ether, the iodide can be easily displaced by triphenylphosphine to give the desired phosphonium salt **87** (92 % yield from **160**).

37.3.3 Final Stages and Completion of the Total Synthesis of Brevetoxin B

A crucial stage in the synthesis of brevetoxin B has been reached. The reactions described thus far have culminated in the syntheses of key building blocks **86** and **87**, each in enantiomerically pure form and of the correct absolute configuration. Taken together, these two fragments comprise ten of the eleven oxacycles contained within the natural product. The synthetic objective is now the convergent union of these two building blocks and the construction of the final ring, namely didehydrooxocane ring H. It will be recalled that the retrosynthetic analysis presented in Scheme 17a identified an intermolecular Wittig reaction^{36b} as a potential method for joining compounds **86** and **87**. The *cis* carbon-carbon double bond that would result from a (*Z*)-stereoselective Wittig reaction between **86** and **87** is found in the natural product and would play a central role in the didehydrooxocane-forming hydroxy dithioketal cyclization. The decision to employ a Wittig reaction to achieve the coupling of fragments **86** and **87** was further reinforced by the well-appreciated fact that the Wittig reaction is a most effective and mild method for the construction of carbon-carbon bonds. In the event, exposure of the phosphorus ylide resulting from the action of *n*-butyllithium on phosphonium iodide **87** to aldehyde **86** at -78°C in THF-HMPA, followed by warming of the reaction mixture to 25 °C, provides the desired coupling product; the stereoisomeric *trans* alkene is not





Scheme 29. Completion of the total synthesis of (+)-brevetoxin B (1).

observed in this reaction (Scheme 29). Compound **85** is then revealed after selective acid-induced solvolytic cleavage of the trimethylsilyl ether (75 % overall yield). Incidentally, the (*Z*) stereoselectivity observed in the Wittig reaction described above depends on the use of HMPA.

With the two oxepane rings and the eight six-membered oxacycles in their proper places, the task of assembling the complex polycyclic framework of brevetoxin B is reduced to the construction of only one C–O bond. At this stage of the synthesis, tension was high because we had never accomplished the construction of an intact brevetoxin B skeleton. As matters transpired, the decision to defer the construction of the didehydrooxocane ring to such an advanced stage in the synthesis proved to be beneficial. Exposure of compound **85** to the conditions of a hydroxy dithioketal cyclization accomplishes the desired ring closure to give, after homolytic reductive cleavage of the ethylthio group with triphenyltin hydride and AIBN, compound **161** in an overall yield of 85 %. It is noteworthy that the Ag⁺-induced hydroxy dithioketal cyclization and the subsequent reductive cleavage of the C–S bond proceed diastereoselectively. The success of the C–S bond cleavage under the mild conditions employed reflects the beneficial effect of the adjacent oxygen in stabilizing the incipient carbon-centered radical involved in this process. The stereochemical outcome of the ring closure and of the reduction (with retention of stereochemistry) are consistent with the results of related model studies¹⁵ (see Scheme 3) and can be explained on kinetic as well as thermodynamic grounds.

With the polycyclic framework of the natural product intact, the completion of the total synthesis only requires a short sequence of reactions. At this juncture, the decision was made to address the problem of reconstituting the A-ring lactone. It was hoped that a selective oxidation of the A-ring allylic ether could be achieved.

As a class, ethers are distinguished by their stability under a wide range of reaction conditions; ethers are, in fact, relatively inert to most reagents. A conspicuous exception to this generalization is the finding that strong oxidants such as the oxides of the transition metals chromium, manganese, and ruthenium can oxidize ethers to esters and lactones.⁶¹ In recent years, such transformations have been conducted with much success, even in the challenging arena of natural products total synthesis. In contrast to saturated ethers, allylic and benzylic ethers are more susceptible to oxidation, an observation that provided a basis for the proposition that it might be possible to achieve a selective oxidation of the A-ring allylic ether in **161** to the corresponding unsaturated lactone. Despite the attractiveness of this oxidation, a careful examination of compound **161** reveals the following problem: compound **161** possesses not one, but two allylic ethers, both of which could be oxidized. A potentially serious regiochemical problem thus presents itself. In the event, however, when compound **161** is exposed to pyridinium chlorochromate (PCC) in benzene at 80 °C, the crucial A-ring oxidation takes place regioselectively to give the desired unsaturated lac-

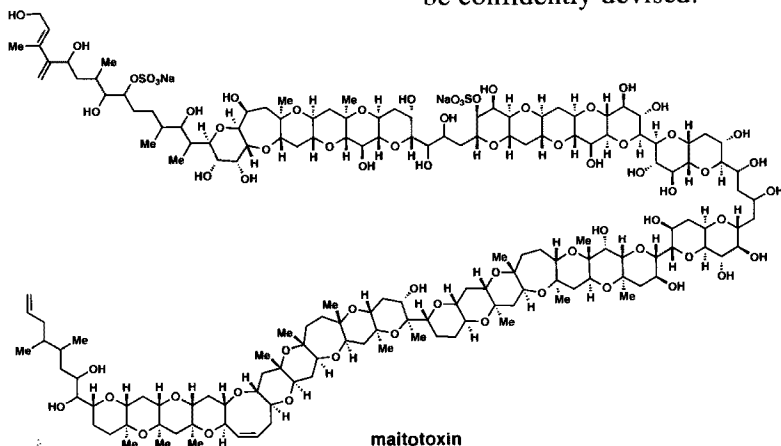
tone; products corresponding to an undesired oxidation at C-29 are not observed, presumably due to the steric congestion of this center. Aldehyde **162** can then be formed after selective fluoride-induced cleavage of the *tert*-butyldiphenylsilyl ether, followed by Dess–Martin oxidation of the resulting primary alcohol.

Only two operations remain. Reaction of the enolic form of aldehyde **162** with Eschenmoser's reagent ($\text{H}_2\text{C}=\text{NMe}_2^+\text{I}^-$)⁶² in the presence of triethylamine provides the desired enal after a simple β -elimination. Finally, cleavage of the remaining *tert*-butyldimethylsilyl ether with $\text{HF}\cdot\text{pyridine}$ completes the total synthesis of (+)-brevetoxin B (**1**).

37.4 Conclusion

The total synthesis of brevetoxin B (**1**)^{6,63} is a major advance in total synthesis, particularly as it is the first synthesis of a highly complex molecule of the brevetoxin class. The necessity for the development of new synthetic technologies for the construction of brevetoxin's ether rings stimulated the invention of several new methods for the synthesis of cyclic ethers of various sizes. Among these are the regio- and stereoselective tetrahydrofuran, tetrahydropyran, and oxepane systems using specifically designed hydroxy epoxides, the hydroxy dithioketal cyclization approach to didehydrooxocanes, the bridging of bis(thiolactones) to bicycles, particularly bis(oxepanes), the bridging of dithioesters to oxepanes, and the TMSOTf-induced hydroxy ketone cyclization to oxepanes.

In addition to the discovery and development of new synthetic methods and strategies, the total synthesis of brevetoxin B (**1**) opened the way for the construction of designed brevetoxins for biological investigations of these fascinating neurotoxins. Furthermore, strategies towards the total synthesis of the more complex relatives of brevetoxin B, ciguatoxin⁶⁴ and maitotoxin⁶⁵ can now be confidently devised.



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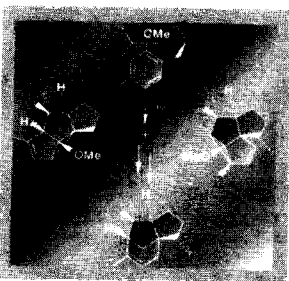
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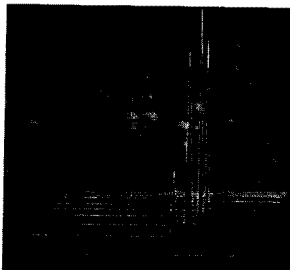
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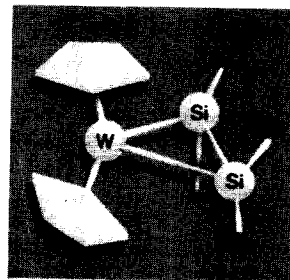
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